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Spontaneous Atherosclerosis in the Rabbit

By JOSEPH H. BRAGDON, M.D.

Microscopic lesions interpreted as representing early atherosclerosis were found in the aortas of most suckling rabbits. This is a period characterized by relatively high plasma lipid levels. In the postweaning period the lesions regressed. Fresh lesions reappeared in a significant number of adult rabbits of both sexes. Correlation with plasma lipid levels in the adult is less conclusive.

THERE exist a few reports of the spontaneous occurrence of grossly visible lipid accumulations in the aortic intima of rabbits. Ophuls[1] reported a single case, that of a "large, healthy, well-developed female raised in the country." Nuzum and co-workers[2] reported six cases among 190 old rabbits that had been used for the standardization of insulin and as "control animals in various experiments." Photomicrographs in both reports clearly indicate that these were instances of rabbit atherosclerosis. But Duff,[3] in a critical review, discredited these cases because of the uncontrolled factors involved, and concluded that there was no positive evidence for a spontaneous form of the disease. The only other relevant report that could be found is that of Solowjew[4] from Anitschkow's laboratory. He examined microscopically the ascending aortas of 10 suckling rabbits 35 to 48 days old, and found sudanophilic material in the intima in six animals. Five control animals six to eight weeks after weaning showed no stainable lipid.

The occurrence or nonoccurrence of spontaneous atherosclerosis in the rabbit is of importance for several reasons. Its purported absence has been cited as evidence of dissimilarity between the rabbit and the human forms of the disease. Its unrecognized presence could lead to false conclusions concerning the pathogenesis of the experimental form of the disease. It is for these reasons that the following report is made.

MATERIALS AND METHODS

All animals examined in this study were born and raised in the rabbit colony of the National Institutes of Health, and were from a well established strain of New Zealand white. The young customarily remain with their dam for eight weeks, during the latter half of which time they gradually wean themselves to a diet of pellets. These are manufactured to specifications from vegetable sources only.* Analysis of one sample yielded: moisture 8 per cent, protein 20 per cent, fat 3.6 per cent, fiber 10.3 per cent, and ash 7.7 per cent.

All bleedings for lipid analyses were performed in the nonfasting state with heparin as the anticoagulant. The blood was centrifuged for 30 minutes at 2500 revolutions per minute, and the plasma extracted in 95 per cent ethanol-ether (3:1). The residue remaining after evaporation of the solvents was then re-extracted in petroleum ether–ether (7:1), and the several lipid fractions determined in aliquots of the latter: free and total cholesterol by the method of Schoenheimer and Sperry[5]; lipid phosphorus by a modification of the method of Fiske and Subbarow[6] (lipid phosphorus times 25 equals phospholipid); and triglycerides by a colorimetric method recently described.[7]

The animals were killed by decapitation or by air embolism. The heart and aorta were removed *en bloc* and the latter irrigated with 0.9 per cent saline solution. Following formalin fixation, the aortic arch was carefully stripped of its adventitia, washed for five seconds in 95 per cent ethanol, and sectioned with the freezing microtome. As an added precau-

From the National Institutes of Health, Bethesda, Md.

* B-B Laboratory Rabbit Diet, Maritime Milling Co., Inc., Buffalo, N.Y.

tion in eliminating artefacts, the microtome blade was washed frequently with ethanol.

It has been repeatedly observed in cholesterol-fed rabbits that grossly visible lesions first appear in specific areas, among which are the mouths of the great vessels. Therefore, in each case sections were cut through the aorta at the origin of the common carotid. By cutting tangentially, sections with characteristic configurations resulted, so that the exact site of each could be readily identified. The illustrations which follow are all of the aortic surface about the mouth of this vessel. The sections were stained routinely with oil red O[8] and hematoxylin and in some cases for cholesterol by the method of Schultz.[9] A total of 63 rabbits has been so examined.

Findings

No stainable lipid was found in the aortas of six fetuses removed near term from two mothers, nor was any found in the aortas of two rabbits killed approximately 12 hours after birth. But focal deposits of sudanophilic material were clearly seen in the aortas of the one rabbit killed at 1 week of age, in two of three rabbits killed at 2 weeks, in two of three rabbits killed at 3 weeks, and in all of five rabbits killed at 4 weeks of age. The lipid was present both within the endothelial cells and, in a more finely divided form, within the intercellular matrix of the underlying intima. Figure 1 (rabbit 420) illustrates a lesion in a 4 week old rabbit.

The plasma of several of these young suckling rabbits was examined. The fetal samples were clear, but in all cases after birth they were visibly lipemic. Chemical analyses, showing that all lipid fractions are significantly elevated compared with the adult, are presented in table 1.

Several specimens of rabbit's milk, obtained by stripping, were analyzed. The cholesterol content, all in the free form, averaged approximately 50 mg. per 100 cc.; the phospholipids, 150 mg. per 100 cc.; and the triglycerides, 12,000 mg. per 100 cc. There was no significant difference between samples collected within 24 hours of delivery, or at one, two, or three weeks thereafter.

Of eight males killed at 8 weeks of age, during all of which time they had been with the dam, the lightest animal in weight (1420 Gm.) showed no stainable lipid, whereas the heaviest (2180 Gm.) showed a significant deposit, as illustrated in figure 2 (rabbit 397). Among the others also, there was a rough correlation between body weight and the amount of lipid seen, suggesting that the most aggressive and persistent sucklings developed the most extensive lesions, while the smaller animals presumably resorted at an earlier age to the pellet diet.

Thirty-five additional animals were examined at intervals ranging from two and one-half weeks to three years after weaning. The results are presented in table 2, and show that the lipid deposited during the suckling period tends to disappear in the weeks immediately following weaning. It disappears first from within the endothelial cells and more slowly from the interstitial matrix of the intima. Most animals examined between two and six weeks after weaning showed no lesions, but in a significant number some lipid persisted in scattered areas within the intima, as illustrated in figure 3 (rabbit 416). The method of removal, either from the endothelial cells or from the interstitial spaces, remains unknown.

It is of some interest that the plasma lipid levels in these young, rapidly growing animals fall to normal soon after weaning. Two animals weaned at 6 weeks of age had normal values for all fractions one week later. This rapid fall is in marked contrast to the behavior of four adult animals in which moderate degrees of hypercholesterolemia (133 to 214 mg. per 100 cc.) were attained by feeding a 0.1 per cent cholesterol diet* over a six week period, after which time six additional weeks elapsed before the plasma cholesterol levels returned to normal.

Whereas the lipid deposits of the suckling period tend to disappear in the weeks immediately following weaning, the data in table 2 indicate that fresh lesions may reappear at any time thereafter. The duration of "adolescence" in these rabbits is unknown, but full sexual maturity usually occurs by 16 weeks of age.

* The cholesterol is dissolved in ether, which is then shaken over the pellets. When the ether evaporates, the cholesterol is left in an amorphous, noncrystalline state. For the rapid production of hypercholesterolemic plasma, the concentration is raised to 1 per cent. Plasma cholesterol levels rise abruptly and grossly visible atherosclerosis develops universally.

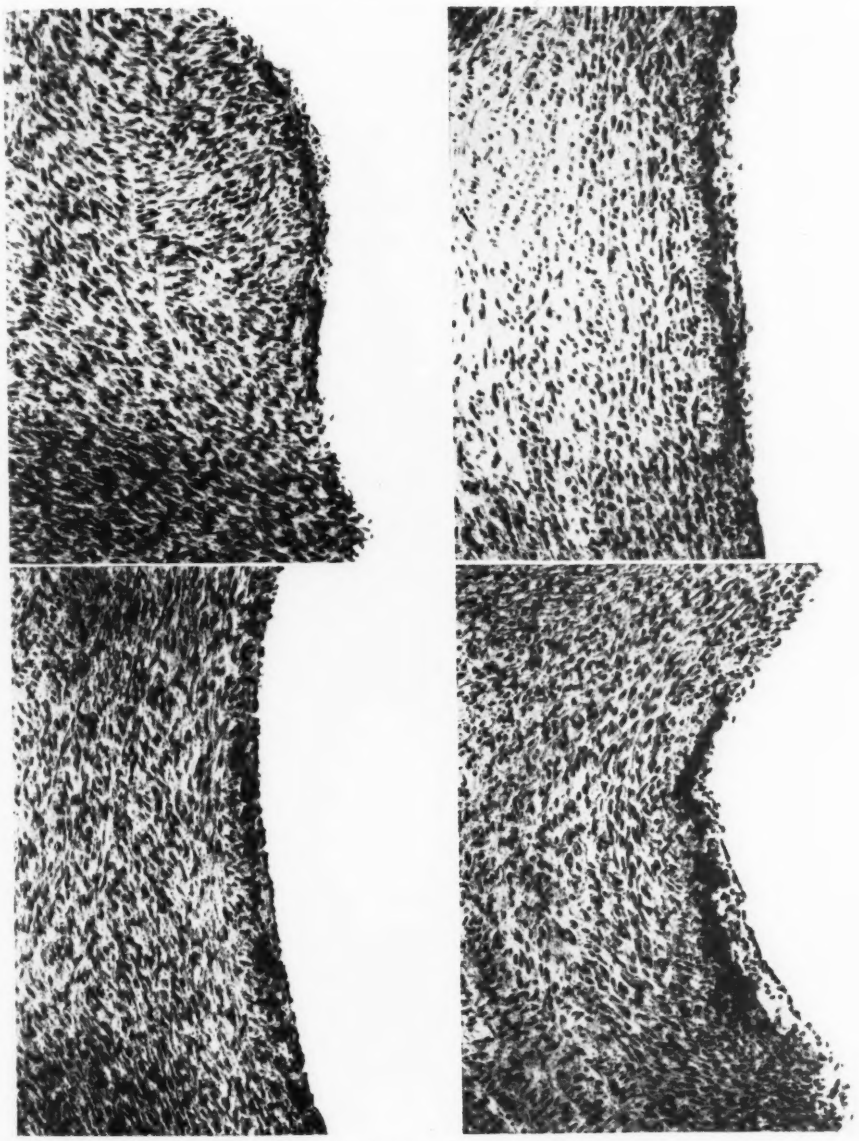

FIG. 1, *top left:* (Rabbit 420) Section showing the aortic surface of the mouth of the common carotid artery of a suckling rabbit 4 weeks old. Lipids are stained red. × 90.

FIG. 2, *top right:* (Rabbit 397) Section from the same area of a weanling rabbit 8 weeks of age. Sudanophilic material can be seen both within the endothelial lining cells, and finely dispersed within the interstitial matrix of the underlying intima. × 90.

FIG. 3, *bottom left:* (Rabbit 416) Section from same area of a female rabbit 6 weeks after weaning. The lipid has disappeared completely from the endothelium and partially from the underlying intima. × 90.

FIG. 4, *bottom right:* (Rabbit 533) Section from the same area of a rabbit 13 weeks after weaning and in the last week of her first pregnancy. There is a considerable accumulation of lipid, predominantly in the intima. This lesion gave a strong positive reaction for cholesterol. × 90.

Figure 4 (rabbit 522) illustrates the most advanced lesion seen in an adult in this series. Because it occurred in a female in the twenty-eighth day of pregnancy (normal gestation period 30 days), two others in the same state were examined. One showed a definite lesion; the other showed none. There are, however, sufficient examples in table 2 to show that fresh lesions in the adult are not limited to the pregnant female.

In only a few cases among the adult group were plasma lipid levels determined, so that no statistically significant correlation with the presence or absence of lesions is possible. In the case of two rabbits, however, both nontional levels were relatively high. Resorption of lesions is a slower process in the adult than in the postweaning period. An objection might be raised that the lipid deposits observed in these rabbits bear no relation to the classic form of experimental atherosclerosis produced by prolonged feeding of cholesterol and characterized by grossly visible lesions containing foam cells, cholesterol crystals, and fibrosis. Such an attitude has occasionally been expressed regarding the "fatty streaks" seen in infants and children in relation to the adult form of the human disease. For this reason, several rabbits in the postweaning period, when spontaneous lesions are least likely, were

TABLE 1.—*Degree of Lipid Deposition and Plasma Lipid Levels in Suckling Rabbits*

Rabbit number	Age	Free Cholesterol	Total Cholesterol	Phospholipid	Triglyceride	Extent of Lesion	
						Endothelium	Intima
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		
Mean normal adult*		17 (s.d.6)	48 (s.d.17)	93 (s.d.23)	137 (s.d.51)	–	–
513A-F pool	fetal	19	68	112	149	–	–
484A-B pool	12 hrs.	68	176	243	354	–	–
484C	1 wk.	60	222	261	214	+	+
484D	2 wk.	57	228	276	348	++	++
484E	3 wk.	76	295	360	268	++	++
484F	4 wk.	78	284	305	329	++	+
442	4 wk.	78	244	259	472	++	+
443	4 wk.	69	226	264	572	++	+

* The cholesterol values are based on 75 bleedings of 47 individuals. They may be compared with those of Payne and Duff[13] based on single bleedings of 42 rabbits: free cholesterol, 19± 9 mg. per 100 cc.; total cholesterol, 46 ± 17 mg. per 100 cc. The values for phospholipid and triglyceride are based on fewer determinations.

pregnant females of the same age, plasma levels were determined on seven occasions over a period of four weeks prior to death. It was fortuitous that one showed consistently low lipid levels and the other consistently high levels. Details are presented in table 3. At necropsy the rabbit with the low levels showed no lesions, whereas the animal with the relatively high levels showed small focal deposits of sudanophilic material. That single determinations may be misleading is illustrated in the case of rabbit 533, which showed the most extensive adult lesions and yet had very low plasma lipid values at death. This animal was killed in the last week of pregnancy, a period characterized in the rabbit by extraordinarily low lipid levels. It is possible that her pregestaplaced on the 1 per cent cholesterol diet and killed from 7 to 14 days later. Lesions indistinguishable from the spontaneous form of the disease, including lipid accumulations within endothelial cells, were universally present. The conclusion, therefore, appears warranted that the difference is one of degree only.

Failure to recognize these spontaneous lesions has apparently led to misinterpretations of the histogenesis of the experimental form of the disease. Duff's illustration,[10] for instance, of the earliest lesion found after feeding cholesterol in olive oil bears a striking resemblance to figure 3 of this paper, which illustrates a normal rabbit six weeks after weaning, and is presumably a late, not an early lesion. Duff did not give the age of his rabbit, but stated

that he intentionally used young animals. It is also possible that claims made regarding the appearance of microscopic quantities of intimal lipid following the intravenous injection of cholesterol sols should be re-examined.

The fact that atherosclerosis develops apparently universally in suckling rabbits in the presence of plasma lipid levels elevated for the rabbit, but within the normal human range, is of interest. In view of recent suggestions[11, 12] that a ratio of cholesterol to phospholipid in excess of unity may be of significance in the pathogenesis of atherosclerosis, it is noteworthy that in the suckling rabbit this ratio is below unity.

The apparent fact that fresh lesions do not develop between weaning and sexual maturity, and the established fact that they may appear in adult rabbits of either sex, remain unexplained. They may possibly be produced by transient periods of mild hypercholesterolemia —for the rabbit.

TABLE 2.—*Degree of Lipid Deposition in Relation to the Postweaning Age*

No.	Sex	Wt.	Age in weeks		Extent of lesion	
			Before weaning	After weaning	Endothelium	Intima
527	M	1200	6	2½	−	−
521	M	1400	6	2½	−	−
522	M	1400	6	2½	−	−
519	M	1400	6	2½	−	−
520	M	1500	6	2½	−	m
523	M	1700	6	2½	−	m
528	M	1400	6	3½	−	−
525	M	1500	6	3½	−	−
526	M	1600	6	3½	−	−
524	M	1600	6	3½	−	m
417	F	2400	8	6	−	m
418	F	2500	8	6	+	+
419	F	2500	8	6	−	m
415	F	2600	8	6	−	−
414	F	2800	8	6	−	−
416	F	2900	8	6	−	+
476	F	3000	8	7	m	+
489	M	1800	6	10	+	m
503	M	1900	4	10	+	+
496	M	1700	4	11	m	−
497	M	1800	4	11	−	−
498	M	1900	4	11	+	+
533	F	3200	8	13*	+	++++
532	F	3300	8	13†	−	m
534	F	3000	8	14	−	m
411	M	3300	4	14	++	++
413	M	2800	4	14	+	+
513	F	4000	8	15*	−	++
535	F	3700	8	18*	−	−
387	F	5100	8	over 2 yrs.‡	−	+
388	F	4300	8	over 2 yrs.‡	−	+
536	F	4600	8	over 2 yrs.‡	−	−
537	F	4800	8	over 2 yrs.‡	+	+
540	M	4100	8	over 2 yrs.	−	+
539	M	3100	8	over 3 yrs.	−	−

m: minimal
* 28 days pregnant
† Pseudo-pregnant
‡ Old breeder

SUMMARY

The findings of Solowjew have been confirmed and extended. Suckling rabbits universally develop focal deposits of sudanophilic material in the aortic intima. This occurs in the presence of elevated plasma lipid levels. During the weeks of rapid growth immediately following weaning, the lipid deposits usually disappear completely. In the sexually mature rabbit of either sex, new lesions may reappear, presumably at any time. As these spontaneous lesions are identical in distribution and in histologic appearance with those produced in the first weeks of experimental cholesterol feeding, they are interpreted as representing early reversible lesions of rabbit atherosclerosis.

The importance of recognizing the spontaneous form of the disease, both in evaluating the significance of rabbit atherosclerosis in rela-

TABLE 3.—*Degree of Lipid Deposition and Mean Plasma Lipid Levels (Seven Determinations over a Four Week Period) in Two Old Female Rabbits*

No.	Free Cholesterol	Total Cholesterol	Phospholipid	Triglyceride	Extent of Lesion	
					Endothelium	Intima
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		
536	11 (s.d. 3)	32 (s.d. 10)	80 (s.d. 14)	106 (s.d. 23)	−	−
537	27 (s.d. 6)	76 (s.d. 7)	124 (s.d. 25)	201 (s.d. 80)	+	+

tion to the human form of the disease, and in interpreting findings following investigative procedures, is discussed.

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Mechanism of Iodide Action on Cholesterol Metabolism

By HELEN B. BROWN, PH.D., AND IRVINE H. PAGE, M.D.

Iodide retards or prevents hypercholesterolemia and the development of experimental atherosclerosis in rabbits. "Protection" is estimated from reduction of plasma and/or hepatic cholesterol. Small doses of iodide do not "protect." Iodide in large doses prevents the hypercholesterolemia resulting from exogenous cholesterol and reduces hepatic cholesterol. This effect is independent of the thyroid gland and is not related to "thyroxin-like" plasma iodine. The influence of iodide on cholesterol metabolism seems to be related to the presence of a butanol-insoluble protein-bound iodine compound in the plasma.

IODIDE is almost traditional in treatment of arteriosclerosis.[1] Its use probably began from a confusion of this condition with tertiary syphilis, and continues here and there, although without convincing clinical demonstration. Its modern use depends in part on the fact that iodide inhibits experimental hypercholesterolemia and atherosclerosis in rabbits.[2-9] The purpose of this study is to explore the mechanism of this action.

A major possibility is that iodide alters thyroid function.[10a] Clinically and experimentally, hypothyroidism is associated with hypercholesterolemia and increased incidence of atherosclerosis,[10b, 11-13] while the reverse seems to be true in spontaneous or induced hyperthyroidism.[5, 8, 14-16] Consequently, one explanation of iodide protection is that it depends on increased formation of thyroxin-like substances.[13] Less obvious is the possibility that the effect of iodide may be independent of thyroid or thyroid-like functions. Thus, Ungar[6] found that iodide protected thyroidectomized cholesterol-fed rabbits. However, such extrathyroidal protection could not be demonstrated by Turner and Khyatt.[17]

In this study we propose (1) to investigate the role of the thyroid gland in iodide protection, (2) to determine minimum protective iodide dosages and plasma iodine levels consistent with protection, and (3) to correlate the several fractions of circulating iodine with concentrations of serum and hepatic cholesterol, by studies in normal and thyroidectomized cholesterol-fed rabbits.

METHOD

1. *Animal Care*

New Zealand white rabbits of uniform stock, 15 to 18 weeks of age (2 to 3 Kg. body weight) were selected, kept in individual cages and fed unrestricted amounts of Pratt's Rabbit Pellets. Their drinking water contained no iodine while the pellets yielded intake of 0.2 to 0.3 mg. of iodide daily.

The experiments were grouped in two series and appropriately subgrouped (table 1). Distribution within groups of five or six (experimental) or three or four (control) as to weight and sex were approximately uniform. Supplementary feedings were given six days a week in gelatin capsules.[18]

Series 1 consisted of eight groups of normal rabbits. The experimental groups were fed 0, 1, 10, 20 or 40 mg. of iodide as potasium iodide and, in the first eight weeks, 200 mg. of cholesterol,* increased to 400 mg. in the subsequent 15 weeks. Control groups received 0, 1 or 20 mg. of iodide and no cholesterol.

Series 2 consisted of thyroidectomized rabbits (experimental) fed 0, 1 or 40 mg. of iodide with 400 mg. of cholesterol for 10 weeks; control groups received iodide without cholesterol or (one group of normal rabbits) cholesterol without iodide.

The animals were weighed weekly. Blood was taken from ear veins, biweekly at first and triweekly

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

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* Cholesterol used in these experiments was very kindly furnished by Dr. Augustus Gibson of Merck and Co.

in the later phases of the study. At the end of the experiment the animals were killed by bleeding and autopsies were performed. Liver, spleen, kidneys, heart and aorta were weighed and sampled for cholesterol analysis. Aortas were sectioned and fixed in formalin for subsequent staining with Sudan IV.

TABLE 1.—*Summary of Experiments*

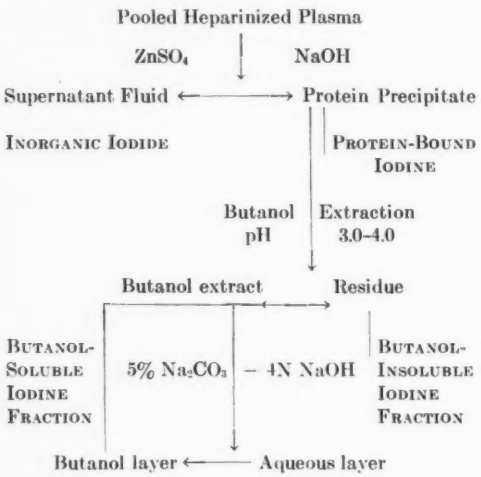
Series I Normal Rabbits								Series II Thyroidectomized Rabbits						
Group	No. of Sex		Daily Intakes (6 × week)		Mean body wt. Kg. weeks			Group	No. of Sex		Daily Intakes (6 × week)		Mean body wt. Kg. weeks	
	M	F	Chol	Iodine	0	8	23		M	F	Chol	Iodine	0	10
			mg.	*mg.*							*mg.*	*mg.*		
1	2	2	0	0	2.5	3.2	3.8	1	2	2	0	0	3.2	3.1
2	1	2	0	1	2.7	3.2	3.9	2	2	1	0	1	3.0	3.0
3	2	1	0	20	2.6	3.2	3.9	3	2	1	0	40	2.8	2.9
4	2	3	400*	0	2.7	3.3	4.1	4†	3	3	400	0	2.8	3.5
5	3	2	400	1	2.5	3.2	4.0	5	3	3	400	0	2.8	2.7
6	3	2	400	10	2.5	3.3	4.0	6	3	2	400	1	3.0	3.2
7	2	3	400	20	2.6	3.2	3.9	7	3	3	400	40	3.0	3.1
8	3	2	400	40	2.6	3.2	3.9							

Age at start, 15–18 weeks
* For eight weeks, cholesterol-fed rabbits received 200 mg. cholesterol daily, then 400 mg. for the following 15 weeks

Age at start, 15–18 weeks
Duration of experiment 10 weeks
† Unoperated control rabbits

2. *Chemical Methods*

Cholesterol determinations were done by the Schoenheimer-Sperry method.[19] The scheme of analysis of plasma iodine fractions is as follows:



Butanol Soluble–Alkali Insoluble Iodine Fraction (Thyroxin-Like)

Procedure. Six 2 ml. samples of heparinized plasma, pooled by groups, were transferred into 40 ml. centrifuge tubes for protein precipitation (Somogyi[20]). The supernatant fluid was decanted after centrifugation and used for direct determination of inorganic iodide.[21]

The separation of fractions was then carried out by a modification of the method of Taurog and Chaikoff.[22] The protein precipitates were thrice washed with 20 ml. redistilled water until the wash was chloride-free. Two precipitates were used for determination of total protein-bound iodine. The four remaining were used for butanol extraction. Butanol extraction of the acidified precipitate was substituted for direct extraction of plasma, since thyroxin- and diiodotyrosine-like iodine fractions are extractable for acidified hydrolysates of thyroid tissue.[23] Precipitates were brought to pH 3 to 4 by addition of 10 per cent sulfuric acid (0.5 ml.) and extracted, first with 25 ml. and twice with 15 ml. portions of butanol, by vigorous hand shaking for one and one-half minutes. Successive butanol extracts of each precipitate were decanted and combined.

Two extracts were made alkaline by addition of 0.5 ml. of a 5 per cent sodium carbonate–4 normal sodium hydroxide mixture and butanol removed by distillation under reduced pressure. The last traces of butanol were removed by addition of 90 per cent ethyl alcohol and re-evaporation. These residues were used for determination of total butanol-soluble iodine. The remaining two butanol extracts were treated with the sodium carbonate–sodium hydroxide mixture (50 ml. and 30 ml. in succeeding ex-

tractions) and used for determination of butanol-soluble alkali-insoluble iodine. The residue remaining after the butanol extraction (freed from butanol traces by evaporation with 90 per cent ethyl alcohol under vacuum, or by the simpler method of washing twice with ethyl ether) was used for analysis of butanol-insoluble iodine. Iodine-free whole wheat flour was used as organic material in ashing the butanol extracts.

Iodine determinations were done by the method of Barker.[24] The time of ceric sulfate reduction was prolonged from 15 to 30 minutes which gave the same range of color change for 0.01 to 0.05 μg. iodine as for 0.02 to 0.10 μg.

A sample of normal dog plasma was fractionated in parallel with each group of samples as a low iodine (2 μg. per 100 ml.) protein-rich reference.

The entire method was tested by recoveries of iodine compounds added to plasma. Ninety-five to 100 per cent potassium iodide and 92 to 94 per cent thyroxin and diiodotyrosine were recovered when any one or a combination of the three were added to the same plasma. Eighty-five to 90 per cent of added thyroxin was obtained by fractionation with no interference from added potassium iodide or diiodotyrosine. These recoveries are similar to those reported by others.[22, 24, 25]

Contamination of the protein precipitate by plasma inorganic iodide after three washings amounted to 0.5 per cent of the inorganic iodide fraction.[26] This occlusion of inorganic iodide leads to an appreciable error only in the determination of protein-bound and butanol-soluble iodine in the thyroidectomized rabbits fed 40 mg. iodine. Results have been corrected for this error (table 5). Fractionation carried out on three-day dialyzed and undialyzed portions of the same plasma containing 3, 18 and 50 μg. per 100 ml. protein-bound iodine and up to 250 μg. per 100 ml. inorganic iodide showed no differences. Further extraction of the residue with three butanol washings removed no more iodine.

Results

1. *Tissue Cholesterol Changes and Iodide*

Under the conditions of these experiments cholesterol feeding did not produce aortic atherosclerosis, gross or microscopic. Plasma and hepatic cholesterol increased; the cholesterol contents of aorta, heart, spleen and kidney remained normal. The protective function of iodide was therefore estimated from its effect on plasma (table 2) and hepatic cholesterol (table 3).

The results in normal rabbits (series 1) were as follows. Iodide alone did not alter the plasma cholesterol level. It did reduce hepatic total and ester cholesterol. Cholesterol feeding alone increased plasma and hepatic cholesterol. Iodide given with cholesterol reduced this hypercholesterolemia at a dosage of 20 mg. and prevented it at 40 mg.; 1 and 10 mg. had no effect during cholesterol feeding. Total and esterified hepatic cholesterol were not changed by 20 and 40 mg. iodide dosages, but 1 and 10 mg. fed with cholesterol increased the proportion of hepatic ester cholesterol.

In the rabbits of series 2, thyroidectomy alone elicited hypercholesterolemia without changing hepatic cholesterol. Iodide did not influence this hypercholesterolemia but did reduce hepatic cholesterol. Cholesterol feeding raised both plasma and hepatic cholesterol; the exogenous hypercholesterolemia was much greater than in normal animals on the same diet. Iodide in amounts of 1 and 40 mg. given with cholesterol reduced exogenous hypercholesterolemia. In contrast to its effect in normal rabbits, iodide reduced hepatic total and esterified cholesterol. Data from series 1 and 2 are summarized in table 4.

The outstanding difference between normal and thyroidectomized rabbits was that 20 or 40 mg. iodide dosages were required to produce significant reduction in plasma or hepatic cholesterol in normal cholesterol-fed animals while 1 mg. was effective after thyroidectomy.

2. *Plasma Iodine Fractions and Iodide*

Iodide administration increased plasma inorganic and total protein-bound iodine in both normal and thyroidectomized rabbits in proportion to dosage (table 5). In normal animals inorganic iodide rose from 2.3 μg. per 100 ml. on the basal diet to 285 on 40 mg., and the protein-bound iodine from 7.1 to 42.3 μg. per 100 ml. The mean increments were greater in thyroidectomized rabbits. One mg. of iodide raised plasma protein-bound iodine to 26 μg. per 100 ml. in thyroidectomized animals as compared with the 20 mg. required to produce the same level in normal animals.

The fractions of the protein-bound iodine are also given in table 5. The butanol-soluble fraction was between 5 and 10 μg. per 100 ml. in all animals on iodide dosages less than 40 mg. The butanol-soluble alkali-insoluble iodine ("thy-

roxin-like") was even more constant, ranging from 4.6 to 7.3 μg. per 100 ml. in normal and thyroidectomized animals independent of iodide dosage. An exception occurred in thyroidectomized animals fed 40 mg. for 10 weeks.

rise in inorganic and protein-bound iodine in both normal and thyroidectomized rabbits. The butanol-soluble fractions, which include the alkali-insoluble iodine, were not altered. Significant decreases in plasma and/or hepatic cho-

TABLE 2.—*Mean Values of Total Plasma Cholesterol*

Group	Daily Intake		Pre-exper. period	Period on 200 mg. chol., 8 weeks	Period on 400 mg. chol., 15 weeks	Comparison between Groups. p values compared with	
	Chol.	Iodide				Normal	Chol. fed
			Series 1. Normal Rabbits				
	mg.	*mg.*	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*		
1	0	0	36 ± 1.7 (35)	33 ± 3.5 (16)	42 ± 3.5 (24)	—	<0.01
2	0	1		31 ± 2.9 (12)	36 ± 3.2 (18)	>0.2	—
3	0	20		36 ± 3.8 (12)	47 ± 6.4 (18)	>0.4	—
4	+	0		37 ± 3.5 (20)	92 ± 11.4 (30)	<0.01	—
5	+	1		40 ± 3.4 (21)	110 ± 10.9 (30)	<0.01	0.2
6	+	10		44 ± 4.5 (18)	69 ± 10.3 (30)	<0.02	>0.10
7	+	20		33 ± 1.8 (15)	57 ± 4.5 (24)	<0.01	<0.01
8	+	40		35 ± 3.8 (20)	47 ± 4.3 (30)	>0.3	<0.01
			Series 2. Thyroidectomized Rabbits				
					Period on 400 mg. chol., 10 weeks	Compared with Series 1 Normal	Compared with Series 2 Chol. fed. thyroidec.
1	0	0	33 ± 3.5 (12)		84 ± 13.8 (23)	0.01	—
2	0	1			95 ± 11.4 (16)	—	—
3	0	40			89 ± 11.5 (18)	—	—
4*	+	0			107 ± 11.8 (34)	—	<0.01
5	+	0			353 ± 46.1 (31)	—	—
6	+	1			217 ± 13.2 (24)	—	<0.02
7	+	40			209 ± 13.5 (32)	—	<0.01

The figures preceded by ± denote the standard error of the mean; those in parentheses, the number of values in the series. The p values are taken from Fisher's table of t. Values obtained on one rabbit are not included in average of group 7, series 1.

* Normal rabbits.

Butanol-insoluble protein-bound iodine accounted for most of the increased protein iodine. Normally none is present. More appeared in thyroidectomized than in normal animals on the same iodide intake; the amount in plasma of thyroidectomized animals on 1 mg. iodide daily was the same as in normals on 20 mg. Thyroidectomized controls had a small amount of this fraction in the plasma which can be attributed to the iodide content of the basal diet (0.2 to 0.3 mg. iodide daily).

Reduction in plasma and/or hepatic cholesterol as described above was accompanied by a lesterol occurred in those animals in which the butanol-insoluble fraction was from 20 to 71 μg. per 100 ml. (table 5).

DISCUSSION

1. *Iodide and Cholesterol Metabolism*

Evaluation of the experimental conditions under which iodide induces changes in cholesterol-fed animals clarifies some of the conflicting reports in the literature. Inorganic and organic iodine compounds fed with cholesterol tend to maintain blood cholesterol at normal levels, reduce hepatic cholesterol and retard or prevent

development of plaques in the aorta of normal rabbits.[2-9] Deposition may be prevented under some circumstances without significant reduction of hyperlipemia.[7]

This action of iodide on cholesterol metabolism depends upon the time it is given. If hypercholesterolemia and atherosclerosis develop before iodide is administered, no fall in cholesterol or regression of lesions occur either in thyroidectomized[15] or normal animals.[14, 15, 27]

The amount of cholesterol in the diet is important. Iodide can only give protection when

TABLE 3.—*Mean Values of Hepatic Total and Ester Cholesterol*

Normal Series 1 Group No.	Thyroidectomized Series 2 Group No.	Diet	Total Cholesterol % fresh tissue		Comparison between Groups. p values compared with	
					Normal	Chol. fed.
1 & 2	1	Normal (and noneffective iodide)	.247 ± .010	(11)	—	<0.01
3	2 & 3	Iodide (effective)	.195 ± .010	(8)	<0.01	—
4	4 & 5	Cholesterol	.359 ± .026	(14)	<0 01	—
5 & 6	—	Cholesterol 1 & 10 mg. iodide	.347 ± .040	(10)	<0.01	0.7
7 & 8	—	Cholesterol 20 & 40 mg. iodide	.432 ± .051	(10)	<0.01	<0.1
—	6 & 7	Cholesterol 1 & 40 mg. iodide	287 ± .190	(10)	<0.05	<0.01
			Esterified Cholesterol % total cholesterol			
1 & 2	1	Normal (and noneffective iodide)	17 ± 3.2	(11)	—	0.01
3	2 & 3	Iodide (effective)	4 ± 1.7	(8)	<0.01	—
4	4 & 5	Cholesterol	32 ± 3.7	(14)	<0.01	—
5 & 6	—	Cholesterol 1 & 10 mg. I	62 ± 6.0	(10)	<0.01	<0.01
7 & 8	—	Cholesterol 20 & 40 mg. I	29 ± 5.7	(10)	0.1	0.7
—	6 & 7	Cholesterol 1 & 40 mg. I	12 ± 4.1	(10)	>0.6	0.01

Because thyroidectomy did not influence hepatic cholesterol, values of both series are grouped for statistical treatment. The figures preceded by ± denote the standard error of the mean; those in parentheses the number of values in the series. The p values are taken from Fisher's table of t. Livers from one rabbit in group 2 and one rabbit in group 6, series 2, were not analyzed.

TABLE 4.—*Summary of Plasma and Hepatic Cholesterol. Alterations from Normal*

Supplement	Normal Rabbits, Cholesterol in		Thyroidectomized Rabbits, Cholesterol in	
	Plasma	Liver	Plasma	Liver
Basal Diet	normal	normal	raised above normal	normal
Iodide 1–10 mg.	normal	normal	same level as basal diet	reduced below normal
Iodide 20–40 mg.	normal	reduced below normal	same level as basal diet	reduced below normal
Cholesterol	raised above normal	raised above normal	raised high above normal	raised above normal
Cholesterol and Iodide 1–10 mg.	same as cholesterol level	same as cholesterol level	reduced below cholesterol level	normal
Cholesterol and Iodide 20–40 mg. I	normal	same as cholesterol level	reduced below cholesterol level	normal

the amounts of cholesterol are not excessive. Usually no protection has been reported when rabbits were fed over 500 mg. a day.[9, 16, 28] Turner and Bidwell[29] found that, on a diet containing 500 mg., the protective effect of iodide was lost within four months. Our rabbits were of iodide to become manifest on blood and hepatic cholesterol. The evidence of these experiments is in favor of the concept that atherosclerosis is reduced in cholesterol and iodide-fed thyroidectomized rabbits[6] and in disagreement with the view[17] that hypercholesterolemia

TABLE 5.—*Blood Plasma Iodine Fractions*
(Mean Values Given in Micrograms per Hundred Milliliters)

Iodide Intake	Inorganic Iodide	Protein-Bound Iodine	Fractions of Protein-Bound Iodine			Plasma and or Hepatic Cholesterol Reduction
			Butanol-Soluble	Butanol-Soluble Alkali-Insoluble	Butanol-Insoluble	
Normal Rabbits						
Normal	2.3	7.1	—	—	—	
Normal	—	8 0	8.0	2.8	0	—
1 mg.	3.3	15.2	—	—	—	
1 mg.	—	13.1	7.0	4.6	5.3	—
10 mg.	38	22.8	—	—	—	
10 mg.	—	23.8	10 9	4.7	13.2	—
20 mg.	87	28 9	—	—	—	
20 mg.	—	29.4	8.8	5.5	19.6	+
40 mg.	285	42.3	—	—	—	
40 mg.		46.0	24.0	5.0	25.0	+
Thyroidectomized Rabbits						
Normal	4.2	9.5	—	—	—	
Normal	—	9.2	6.0	5.6	4.1	—
1 mg.	63	25.7	—	—	—	
1 mg.	—	25.6	7.7	5.3	20.9	+
40 mg.	2000	65.0*	—	—	—	
40 mg. 8 wks.	—	58 9*	14.2*	7.3	43.3	+
40 mg. 10 wks.	3000	94.0*	26.5*	16.2	71.2	+

Inorganic and protein-bound iodine values are averages of 20 to 30 individual determinations. Fraction averages are of 2 to 4 pools of 10 to 12 individual plasmas taken at various times from rabbits in the same group.
* Corrected for inorganic iodide remaining after three washings of protein precipitate.

more resistant to the effects of cholesterol feeding in that 400 mg. daily did not elicit atherosclerosis after 15 weeks.

The species of experimental animal is also important in the action of iodide on cholesterol metabolism. Chickens are more sensitive to cholesterol feeding than rabbits and develop atherosclerosis on minimum amounts.[30] They show no reduction of plasma cholesterol and only slight reduction in the size of aortic plaques on very large amounts of iodide fed along with cholesterol.[31]

Our experiments show that the presence of the thyroid gland is not necessary for the effect and atherosclerosis are unaffected in such animals.

The increased sensitivity of thyroidectomized rabbits to iodide feeding remains unexplained except as it represents impaired ability to remove iodine from circulation in absence of the thyroid gland.

Differences in iodide requirement of normal and thyroidectomized rabbits emphasize the importance of iodide dosage. In normal animals fairly large amounts of iodide are required to reduce plasma and/or hepatic cholesterol. Minimum reduction was obtained on 20 to 25 mg. iodide daily. A maximum effect may be ob-

tained on less than 100 mg. iodide a day. Forty (reported here) to 80 mg.[8] were about as effective as 382.[5]

These results with large amounts of iodide contrast with the increased plasma and hepatic cholesterol and accelerated aortic deposition produced by 1 to 10 mg.[8, 32] in normal animals. In our own experiments, 1 and 10 mg. increased only hepatic esterified cholesterol significantly. The nature of this paradoxic response to small iodide dosage is not apparent.

Specific aspects of the action of iodide on cholesterol metabolism can be noted. First, iodide in large dosages depresses or prevents hypercholesterolemia of exogenous origin while it does not prevent endogenous hypercholesterolemia elicited by thyroidectomy.

Second, iodide reduces hepatic cholesterol. Although large dosages of iodide did not change hepatic total cholesterol in normal cholesterol-fed rabbits, decreases in hepatic cholesterol were observed in all other iodide-treated groups. The difference between normal and thyroidectomized rabbits fed cholesterol and iodide may be attributable to the greater sensitivity of thyroidectomized animals to iodide. But this explanation does not account for the decreased hepatic cholesterol in normal rabbits fed iodide without cholesterol. The lack of hepatic response of cholesterol-fed normal rabbits to iodide is more likely the result of an equilibrium between inverse effects on hepatic cholesterol of large and small amounts of iodide.

Third, iodide reduces hepatic esterified cholesterol to such an extent that only free cholesterol was present in the livers of over half the iodide-fed rabbits showing reduced total hepatic cholesterol.

Lastly, plasma cholesterol rise is controlled only with simultaneous iodide and cholesterol feeding. Iodide does not alter plasma cholesterol in normal animals, in thyroidectomized hypercholesterolemic rabbits, or in rabbits with hypercholesterolemia present before iodide feeding.

These changes in cholesterol metabolism due to iodide are distinct from those due to thyroidal hormone. The thyroid depresses hypercholesterolemia, either exogenous or endogenous, without a significant effect on the cholesterol content of the whole body or the liver.[33-37]

2. *Iodide and Plasma Iodine*

Plasma inorganic and protein-bound iodine increased in both thyroidectomized and intact animals receiving iodide (table 5). Normally, iodine in the blood of animals and human beings on a low iodine diet consists of a few μg. per 100 ml. in inorganic and protein-bound form.[10c] The protein-bound iodine can be extracted from plasma with butanol and separated into a diiodotyrosine-like fraction, soluble in strong alkali, and a thyroxin-like portion, insoluble in alkali. These fractions have been characterized chemically[22] and chromatographically.[38-40] When no excess iodine has been ingested, the protein-bound iodine is almost entirely thyroxin-like and varies with thyroid activity.[10d] But when iodides are administered, the thyroxin-like portion remains low even though the inorganic and total protein-bound iodine greatly increase. This phenomenon has been observed in patients.[25, 41, 42]

The same is true in rabbits. The "thyroxin-like" iodine fraction amounted to 4 to 7 μg. per 100 ml. in the plasma of our iodide-fed rabbits, both normal and thyroidectomized. It fell within the normal range of plasma protein-bound iodine found in human beings,[43] 85 per cent or more of which consists of "thyroxin-like" iodine.[10d] However, this fraction is very high in our thyroidectomized rabbits when compared with 1 μg. per 100 ml. plasma protein-bound iodine found by others in thyroidectomized animals on a normal diet.[44]

The nature of this butanol soluble-alkali insoluble iodine in the plasma of our iodide-fed rabbits is unknown and its thyroxin content is not yet evaluated. A major portion is probably inactive as judged by the large amount (5.6 μg. per 100 ml.) present in the thyroidectomized animals on the basal diet. Certainly changes in cholesterol metabolism do not appear to be related to this fraction, because the same amount was present in plasma of all iodide-fed animals, whether plasma and/or hepatic cholesterol was significantly reduced or not.

In contrast, the butanol-insoluble fraction of the protein-bound iodine occurs in large

amounts in plasma of rabbits treated with iodide and increases directly with increasing iodide dosage. It is distinct from the "hormonal" iodine.[10c] The thyroid gland contains a butanol-insoluble iodinated protein which yields butanol soluble–alkali insoluble iodine on hydrolysis.[45] However, we were unable to recover this latter substance from plasma. We are conducting further studies on its chemical nature.

Butanol-insoluble iodine is present in animal tissues, other than the thyroid and plasma, as a result of normal metabolism of iodine compounds. Gross and Leblond[46] found radioactive butanol-insoluble iodine metabolites in all tissues, notably in the liver, of rats given radioactive thyroxin. These metabolites disappeared more slowly from the tissues than the butanol-soluble ones. Possibly they are produced in sufficient quantity with prolonged iodine intake to accumulate in the plasma as well as in the tissues. A decrease in plasma and/or hepatic cholesterol with a rise in butanol-insoluble iodine suggests a relationship between the two. This would explain the difference in effective iodide dosage between normal and thyroidectomized rabbits described above. The relationship between this fraction and cholesterol metabolism in cholesterol-fed rabbits is such as to suggest that the protective action of iodide in arteriosclerosis may be related to establishment of adequate plasma and tissue concentrations of butanol-insoluble protein-bound iodine.

Summary and Conclusions

1. The effects of graded dosages of potassium iodide on blood and tissue cholesterol and the plasma iodine fractions in normal and thyroidectomized cholesterol-fed rabbits have been evaluated.

2. A "protective" effect of iodide against cholesterol deposition was estimated from reduction of plasma and/or hepatic cholesterol. In both normal and thyroidectomized rabbits: (a) iodide reduced total hepatic cholesterol without affecting the plasma content; (b) cholesterol feeding increased plasma and hepatic cholesterol; (c) iodide fed with cholesterol counteracted these increases; (d) esterified hepatic cholesterol varied as the total cholesterol.

3. Thyroidectomized rabbits were more sensitive than normal to the effect of iodide on exogenous cholesterol.

4. The endogenous hypercholesterolemia resulting from thyroidectomy was not affected by iodide.

5. Plasma inorganic and protein-bound iodine increased in proportion to the iodide dosage, more so in thyroidectomized than in normal rabbits. Fractionation of the protein-bound iodine showed that the butanol-soluble, alkali-insoluble iodine remained the same in all iodide-fed rabbits. The butanol-insoluble fraction accounted for the progressive increase in protein bound iodine.

6. In animals in which iodide decreased plasma and/or hepatic cholesterol, the butanol-insoluble fraction was present in amounts of 20 μg. per 100 ml. or more.

7. The effect of iodide on cholesterol metabolism is independent of the thyroid gland; it is manifest after thyroidectomy; it is not related to the "thyroxin-like" plasma iodine; the iodide effect is expressed primarily on hepatic cholesterol while a thyroidal action is not.

8. The protective action of iodide against atherosclerosis seems to be related to the presence of a butanol-insoluble iodine compound in the plasma which may act by altering hepatic cholesterol metabolism.

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Changes in Excretion of Intestinal Cholesterol and Sterol Digitonides in Hyper- and Hypothyroidism

By MEYER FRIEDMAN, M.D., SANFORD O. BYERS, Ph.D., AND RAY H. ROSENMAN, M.D.

The fecal output of cholesterol and of noncholesterol sterols was determined in hyper- and hypothyroid rats, and in a group of control animals. The intestinal excretion of cholesterol and of total digitonin-precipitable sterols was found to be considerably increased in the hyperthyroid, and considerably decreased in the hypothyroid animals. The relationship of these findings to the altered plasma cholesterol content occurring in deranged thyroid states is discussed.

RECENTLY, a series of studies[1-3] from this laboratory demonstrated that the source of the plasma cholesterol was the liver. Even more interesting perhaps, was the observation[4] that the rate of cholesterol synthesis by the liver could be gaged by estimation of the daily biliary cholesterol. Thus, a means was provided by which rather exact information concerning the rate of cholesterol synthesis could be obtained in the intact animal.

At the time that these observations were being made, associated studies of hyper- and hypothyroid rats revealed some interesting results. First, it was discovered[5] that the biliary excretion of cholesterol was markedly increased and decreased in hyper- and hypothyroid rats, respectively. Secondly, it was found[6] that cholesterol accumulated in the plasma after biliary obstruction far more rapidly in the hyperthyroid rat than it did in the plasma of the eu- or hypothyroid rat. These two findings, when considered in the light of the earlier observations described above, seemed to permit but one conclusion, namely that a *marked increase in the rate of hepatic synthesis of cholesterol is present in the hyperthyroid rat and the converse in the hypothyroid rat.*

Despite this increased rate of synthesis of cholesterol in the hyperthyroid state (and the opposite in the hypothyroid state), no increase has been observed in the concentration of cholesterol either in the tissues[7] or in the blood of the hyperthyroid animal.[5, 6] Therefore, it would seem likely that the rate of cholesterol excretion and/or destruction must also be more rapid in the hyperthyroid state (and retarded, on the other hand, in the hypothyroid state). The results of the present study do indeed indicate that the rate of excretion of cholesterol is increased in the hyperthyroid rat.

METHODS

(1) *Physiologic.* A series of 29 male rats (Long Evans strain), approximately 12 weeks old, was divided into three groups. Each group was fed a basic laboratory diet of Purina laboratory chow. However, group I (nine rats) also was given desiccated thyroid substance* in the diet (0.3 per cent of basic diet). Group II (10 rats) was given thiouracil* in the diet (0.3 per cent of basic diet). Group III (10 rats) received only the basic diet and served as the controls. This type of feeding resulted in the production of marked hyperthyroidism in group I and hypothyroidism in group II, as previously shown.[6]

Eight weeks after this type of feeding had been instituted, each group of rats was placed in Bollman rat cages,[8] supplied a sterol free diet,[4] and the stools of each rat were collected separately for 72 hours. Rats of groups I and II continued to receive thyroid substance and thiouracil, respectively, during the collection. At the end of the collection period, the animals were killed, and the intestinal contents were collected and added to the stool specimen.

From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, Calif.

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(2) *Chemical.* Because a large portion of cholesterol in the intestine is changed to coprosterol,[9] the stools were assayed not only for total cholesterol but also for all sterols precipitated by digitonin. In this manner, an estimate could be obtained of the actual amount of cholesterol *originally* excreted as such into the intestine.

The stools, together with the expressed intestinal contents of each rat, were placed in individual containers and dried at 60 C. for 48 hours. Thus, all sterol percentages are expressed as milligrams per 100 Gm. of fecal material so collected and dried.

The total dry collection from each animal was ground in a mortar until powdered. Samples of approximately 0.25 Gm. were weighed in Erlenmeyer flasks of 400 ml. volume and the sterols extracted by refluxing with 50 ml. of 1:1 alcohol-acetone mixture for three hours. The extract then was filtered into a 50 ml. volumetric flask, the residue being washed three times with 5 ml. portions of alcohol-acetone. If necessary, the filtrate was partially evaporated between washings to accommodate the volume of wash fluid.

Five ml. portions of the 50 ml. volume of extract were hydrolyzed at 40 C. in a sand bath in a sealed container by incubating for 40 minutes with 5 drops of 5 per cent potassium hydroxide according to the method of Schoenheimer and Sperry.[10] The hydrolyzate was neutralized with 10 per cent acetic acid, using 1 drop in excess and then precipitated with 7 ml. of a clear solution of digitonin in alcohol as described in a previous paper.[1] After standing overnight, the precipitate was transferred quantitatively and filtered through a weighed, sintered porcelain crucible of 1 ml. capacity, washed with a saturated solution of cholesterol digitonide and, finally, once with ether. The value for total digitonin-precipitable sterols was calculated from the precipitate weight and known weight of cholesterol precipitated by a given weight of our digitonin, assuming that noncholesterol sterols precipitated with digitonin in the same ratio by weight as cholesterol.

The entire crucible plus the precipitate then was placed in a test tube (20 by 150 mm.) and the precipitate dissolved in acetic anhydride–dioxane mixture. The acetic anhydride–dioxane solution of sterol digitonide was transferred quantitatively to a colorimeter tube using fresh acetic anhydride–dioxane as wash fluid, and the cholesterol color developed with sulfuric acid. Exact details of these latter procedures have been given in a previous paper.[1] The weight of the noncholesterol sterols was determined by subtracting the assayed weight of cholesterol in the digitonin precipitate from the weight of the total sterol.

TABLE 1.—*Intestinal Excretion of Cholesterol and Sterol Digitonides*

Type of Rat	No. Rats	Average Weight	72 Hour Intestinal Collection						
			Dry Weight	Cholesterol		Non-Cholesterol Sterol		Total Sterol	
				mg. %	mg./72 hrs.	mg. %	mg./72 hrs.	mg. %	mg./72 hrs.
		Gm.	*Gm.*						
Hyperthyroid	9	181 (157–220)*	4.93 (3.5–6.3)	454 (370–620)	22 (15–27) ±1.55†	453 (290–770)	22 (13–29) ±1.63	890 (690–1390)	44 (31–56) ±2.52
Hypothyroid	10	258 (183–328)	1.8 (0.7–2.8)	687 (540–950)	12 (6–20) ±1.28	310 (110–560)	5 (1–9) ±0.9	997 (690–1260)	17 (8–27) ±1.56
Control	10	251 (205–318)	3.64 (2.2–5.3)	398 (340–500)	15 (9–20) ±1.25	425 (220–840)	15 (8–28) ±1.75	826 (600–1280)	30 (18–38) ±2.52

* Range of values

† Standard error of the mean

RESULTS

As table 1 demonstrates, the hyperthyroid rat excretes considerably more cholesterol than the normal rat. Furthermore, his noncholesterol sterol excretion is significantly greater than that of the normal rat. Since this latter contains the coprosterol of the stool, which is believed to be derived from cholesterol,[9] it can be seen that the hyperthyroid rat is excreting considerably more cholesterol than the normal rat. Moreover, this cholesterol is coming from endogenous sources since the animal received no sterol in his food during the feces collection period.

On the other hand, the hypothyroid rat was found to excrete considerably less noncholesterol sterol (see table 1) than the normal or

hyperthyroid rat. His actual cholesterol excretion, however, was not markedly reduced. This may be due to the fact that the general sluggishness of his intestinal activity allowed far more time for the conversion of cholesterol to coprosterol. It is of interest that the actual amount of cholesterol and sterol per gram of stool is not reduced but rather that the amount of stool itself is considerably reduced.

Discussion

The discovery of the marked increase in biliary cholesterol excretion in the hyperthyroid rat, and the converse in the hypothyroid rat,[5] appeared to us to present possible clues, not only about the state of cholesterol metabolism in these two opposing situations, but also about the significance and relationship of bile cholesterol to hepatic synthesis of cholesterol. Subsequent studies have confirmed this earlier belief, for one study[6] has indicated that the rate of cholesterol synthesis is increased in the hyperthyroid rat. A later study,[4] in turn, made it clear that the rate of biliary cholsterol excretion may be employed as a measure of the rate of hepatic synthesis of cholesterol.

Although our observations,[5, 6] suggested an increased rate of cholesterol synthesis in hyperthyroidism (and the reverse in hypothyroidism), little information was gained about the rate of cholesterol excretion in disturbed thyroid states. The present study, however, demonstrates a marked increase in intestinal excretion of cholesterol and sterol digitonides in the hyperthyroid state. The hypothyroid rat, on the other hand, was found to have considerably less fecal sterol than the euthyroid rat, and possibly less unchanged cholesterol. These changes in the content of fecal cholesterol and sterol considerably exceed the differences which might be expected to occur as a result of the previously observed changes[5, 6] in the biliary excretion of cholesterol in these two states.

The magnitude of the increased intestinal excretion of cholesterol and sterols (derived in part from cholesterol) in the hyperthyroid rat, when conjoined with that amount of cholesterol excreted in its bile,[5, 6] further attests to the presence of an increased rate of cholesterol synthesis in this type of thyroid derangement. Thus, if no abnormal decrease has been found in the tissue cholesterol[7] and only a moderate one in the plasma of the hyperthyroid rat,[6] despite the increased intestinal loss of cholesterol, then an increase in the rate of cholesterol synthesis would seem likely. As demonstrated previously,[1-3] the chief site of this increased synthesis of plasma cholesterol is the liver.

Despite the increase in the rate of hepatic synthesis of cholesterol in the hyperthyroid rat, its plasma cholesterol concentration tends to be lowered.[6] This last finding may be due to the fact that the increased intestinal excretion is relatively greater than the increased rate of hepatic synthesis. It is conceivable, moreover, that the increase in hepatic synthesis of cholesterol represents the response of the liver to a plasma being deprived more rapidly than normal of its cholesterol through an increased intestinal excretion and possibly, too, by an increased rate of destruction in the tissues of the body.

Summary

The intestinal excretion of cholesterol and noncholesterol sterol was found to be increased in the hyperthyroid rat. The converse was found in respect to noncholesterol sterol in the hypothyroid rat. These findings furnish confirmation of the previously observed increased rate of hepatic synthesis of cholesterol in the hyperthyroid rat and the decreased rate of such synthesis in the hypothyroid rat.

Acknowledgments

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Intra-arterial Histamine in the Treatment of Occlusive Peripheral Arterial Disease

By JOHN A. DIXON, M.D., W. J. MERLE SCOTT, M.D., AND MARVIN A. EPSTEIN, M.D.

Intra-arterial histamine was found to increase significantly the walking tolerance of a small series of cases of obliterative peripheral arterial disease with intermittent claudication. Physiologic determinations during injection show tachycardia, increased cardiac output, increased stroke volume and increased homolateral femoral arteriovenous oxygen difference. The similarity of these results to those caused by arteriovenous fistulas is noted.

ONE of the most vexing problems with which physicians have to deal is that of intermittent claudication and ischemic changes of the lower extremities in the middle-aged or elderly patient. These individuals are frequently so incapacitated by pains in their legs that they are unable to continue productive activities. Priscoline[1] and occasionally sympathectomy[2] offer some relief to a certain number of these people, but there still remains a large group that cannot be helped by these measures. Priscoline is not well tolerated in some patients and is ineffective in many others. Sympathectomy is not advisable many times because of the lack of favorable responses to the usual presumptive tests of sympathetic paralysis, or by coexistent cardiac, renal or respiratory diseases. This operation involves a definite risk to these older patients. Some patients have had sympathectomy with no relief or a temporary improvement followed by a return of distress.

A nonoperative treatment which would dilate the collateral circulation and could be repeated according to the patient's needs would be valuable. Mufson[3] reported a series of cases with obliterative arterial disease of the lower extremities in which he injected histamine into the femoral artery with favorable results in 84 per cent of the group. It was largely at the insistence of one of our patients who had not been helped by the usual measures that our first intra-arterial histamine injections were tried. The results appeared sufficiently encouraging to be pursued further. This paper is a report of the clinical results obtained in a small series of carefully studied patients with some observations on the physiologic effects of intra-arterial histamine.

From the Departments of Surgery and Medicine, University of Rochester, School of Medicine & Dentistry, and Strong Memorial Hospital, Rochester, N. Y. Supported in part by the Office of Naval Research, under contract with the Department of Medicine, University of Rochester, School of Medicine & Dentistry.

METHODS AND MATERIALS

Eight male patients with intermittent claudication were studied. The average age was 64 years. The patients were selected from a group of more or less chronic clinic visitors who had been refractory to the usual therapeutic measures. They had all been been under observation for a period of several months during which time Buerger's exercises, oral Priscoline, reduction in smoking, moderate doses of alcohol, foot hygiene and reflex heat all had been instituted. Unfortunately, treadmill exercise tolerances were not available on these patients during this period of conservative therapy, but it was the opinion of all observers that maximum benefit from these measures had been attained for a period of time prior to the institution of histamine therapy. Prior to injections, the subjects were taken to a constant temperature room and their skin temperature response in the lower extremities to immersing the arms in hot water was measured. If the temperature in the affected leg did not rise significantly, a posterior tibial nerve block was performed with 1 per cent Novocain and the temperatures again measured. On several of the patients a paravertebral block or spinal anesthetic was given as a further check. All of the patients selected for intra-arterial histamine showed very little temperature response with these procedures, and their ischemia was believed to be on the basis solely of arterial occlusion rather than spasm.

It was thought desirable to have an objective controlled method of following the walking tolerance of these patients rather than to depend upon the usual

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It was thought desirable to have an objective controlled method of following the walking tolerance of these patients rather than to depend upon the usual

statement of the number of blocks walked without pain. A motor-driven continuous belt type treadmill was used which ran at a constant speed of 1.78 miles per hour. The walking surface was inclined to a 10 per cent grade. The grade not only brought out the claudication more sharply, but it also prevented walking with the knee and ankle in a fixed position so that the calf muscles would not become fatigued. It was calculated that walking 10 minutes on this device would be the equivalent of climbing 19 flights of stairs with an eight foot elevation per flight in the same period. Patients were instructed to walk until the appearance of definite claudication of the type usually noted in their ordinary activities. This time was taken as their walking tolerance. The pain end point was surprisingly distinct in most patients.

The histamine injections were given using ordinary intravenous apparatus and a hand bulb to raise

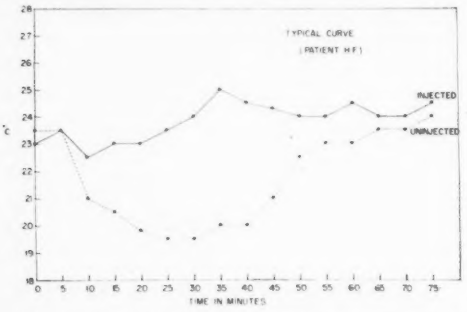

FIG. 1. Typical skin temperature curve during injection in horizontal position showing gradual temperature rise in injected leg and fall in uninjected leg.

the pressure in the bottle, after the method described by Mufson.[3] Three mg. of histamine diphosphate in 500 cc. of normal saline were given into the femoral artery over a period of approximately one-half hour.

It would, of course, have been desirable to have run a control series of placebo intra-arterial injections. With this in mind, several intra-arterial injections of normal saline were given. No alteration in claudication distance was noted following such injections. After receiving a histamine injection, with its attendant warmth and erythema, the patients readily detected subsequent saline injections, thus negating the value of this form of investigation. Further placebo injections were not carried out for lack of an adequately impressive safe substitute injectant.

The usual therapeutic schedule was two injections per week for the first three weeks, then one injection per week until the walking tolerance appeared to have stabilized. Injections were discontinued then and the patient's walking tolerance checked at monthly intervals. If regression was noted, injections weekly were then reinstituted. Patients were all followed for a minimum of five months.

RESULTS

The immediate effects of intra-arterial histamine are usually rather striking. There is first an erythema which appears rapidly and roughly corresponds to the distribution of the main unobstructed arteries. Following this there is an intense pilomotor reaction with the hair on the leg "standing on end." Shortly following this, scattered areas showing wheal formation appear. In patients with occlusion of a major vessel, such as the popliteal, the changes described appear rapidly in the thigh and knee in the region of the genicular anastomoses, then slowly extend down over the calf and foot. The veins uniformly become distended and very prominent, accompanying the erythema.

The thigh skin temperature increases early, but it was found that the temperature of the toes would usually increase very little or might even decrease initially. In several patients the circulation in the foot during the early part of the injection appeared to be somewhat further impaired. This was evidenced by mild cyanosis, mottling and a concomitant fall in skin temperature. This would suggest that initially the capillary flow was actually decreased. However, this phase was always transitory and followed immediately by the typical erythema and increase in skin temperature. Even after a good erythema had appeared in the foot, the skin temperature frequently did not rise significantly in the recumbent position. A typical response to injection in the recumbent position is seen in figure 1. The marked effects of posture on the skin temperatures of the toes during injection is seen in figure 2. Along with the elevation in temperature, the color of the skin of the toes changed to a much brighter pink on standing.

The results of the walking tolerance tests appear in figure 3. Unfortunately, in two of our patients the treadmill was not available to take walking tolerance prior to injection. The initial time which appears on the graph is calculated from their history and is indicated in both cases. All of the patients except one (F.B.) showed a definite increase in their walking tolerance.

Of the seven patients given a course of hista-

mine injections, five were considered to have a "good" result, one a "fair" result and one a "poor" result, or almost no change in walking tolerance. It is very difficult to classify results in patients with intermittent claudication as to whether their response to therapy has been good, fair or poor on the basis of changes in walking tolerance alone because of the wide difference in demands of the individual. For instance, one patient (J.W.) is classified as a good result even though his tolerance increased by only two minutes. He is a moderately severe cardiac and his activities are limited. The small increment in walking tolerance which occurred

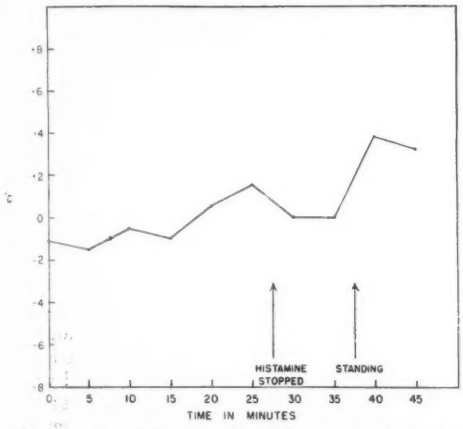

FIG. 2. Composite graph (eight patients) of skin temperature difference of injected leg compared with uninjected leg showing marked rise in temperature on standing.

during treatment was sufficient to practically eliminate symptoms referable to his legs. By the same token, one patient (A.W.) is classified as a fair result even though he nearly doubled his walking tolerance because he is younger, more active, and his legs still cause him some distress in his regular activities. One patient who does not appear in the clinical table of results is worthy of mention. He is a 68 year old white male who had had a midthigh amputation on the left for gangrene, and at the time we saw him had several small gangrenous areas on the toes of his right foot. He was in constant pain and was unable to tolerate even the slightest pressure on his toes. The nailbeds were infected and necrotic. Amputation appeared imminent, but a trial of intra-arterial histamine was instituted. Though some increased pain was noted in the leg during the period of the first injection, later that same day he had almost complete and permanent relief from the severe pain in the foot. Following subsequent injections the gangrenous area disappeared and his nails have shown definite evidence of new growth. In the first injection there was no erythema noted below the knee. With subsequent injections his foot still became blue initially, but a good erythema developed in the lower leg and spread to the foot.

Though it is difficult to be certain in so small a series of cases, it appears that those individuals who are going to be appreciably helped by

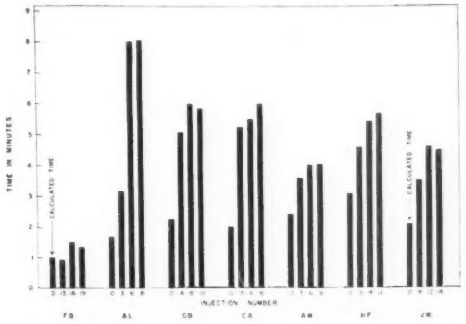

FIG. 3. Walking tolerance time on treadmill and number of injections given. Early and marked increase in tolerance is shown.

histamine injections show definite evidence of increased walking tolerance by approximately the sixth injection. The appearance of good erythema below the knee during the first injection is a good prognostic sign.

PHYSIOLOGIC STUDIES

When it became evident early in the course of this study that some beneficial results were being obtained, a number of procedures were carried out to determine some of the physiologic effects of intra-arterial histamine and gain information concerning its possible mode of action in peripheral arterial disease. The effects of intravenous and subcutaneous histamine in man have been extensively studied and an excellent review of the subject was recently published.[4] In general, intravenous

histamine causes an increase in heart rate, a decrease in stroke volume, a moderate increase in minute volume, and a slight fall in systolic and diastolic blood pressure. The arteriovenous oxygen difference is increased.[5] Peripherally it produces arteriolar dilatation, dilatation of the capillary bed and venules, and mild constriction of larger veins and arteries.[6, 7] There are no reports on the corresponding effects of intra-arterial histamine.

Methods and Materials

The subjects were five of the patients with peripheral vascular disease, and one young man convalescing from a minor surgical procedure. Seven experiments in all were done to determine the effects of intra-arterial histamine on the heart rate, stroke volume and arterial pressure. The subjects were allowed to recline on a high frequency undamped ballistocardiograph (BCG) table, as has been described elsewhere.[8] A chest pneumograph and electrocardiographic (ECG) electrodes were applied. The subject was then rested for 15 to 20 minutes, during which time the control ballistocardiogram, electrocardiogram, and respiratory curve were recorded. The ballistocardiogram was picked up with either a variable capacitance transducer[9] or a piston type strain gage.[10] No amplification was required with the latter method. The records were made with Sanborn & Hathaway mirror galvanometers on direct positive recording paper.

At the end of the rest period the arterial puncture was made, and in three patients a control direct arterial pressure was recorded before beginning the histamine injection. In others the histamine was begun as soon as the puncture was completed. For the pressure records a Statham fluid pressure gage was attached to the intra-arterial needle by a 10 cm. piece of polythene tubing. The system was flushed with heparinized saline, a record taken and the histamine started.

Records were then taken about every eight minutes until the histamine was finished. The same amount, concentration, and speed of injection were used as in the purely therapeutic infusions. In four of the subjects tracings were taken before, during and after a pneumatic cuff was inflated, first on the injected, and then on the other leg. This cuff was placed just below the inguinal region and inflated to 100 mm. Hg. The histamine infusion usually lasted about 25 minutes. In the subjects in whom femoral pressure was recorded, the needle was kept open with heparinized saline after the histamine was stopped, and an arterial pressure record taken 5 to 10 minutes after the infusion was over. In the others the needle was withdrawn as soon as the infusion was finished. After removing the needle the patient remained on the table for 10 to 15 minutes more for recovery records of the ballistocardiogram, electrocardiogram and respirations. The experiment was concluded when these were taken. Blood pressures were determined by the auscultatory method in the right arm at about 10-minute intervals during six of the experiments.

The stroke volume and cardiac output (minute volume) were calculated from the ballistocardiographic record using the area formula of Tanner.[11] This is: Stroke volume in cubic centimeters = $100 \sqrt{(2I \text{ area} + J \text{ area})} \sqrt{C}$. Representative inspiratory and expiratory complexes, usually the largest and smallest, respectively, were measured for each period of the experiment. Where there was marked variation in complex amplitude from one respiration to the next, several additional complexes were measured and averaged. In each record the amplitudes were corrected back to a 1 cm. weight standardization (baseline deflection of 1 cm. when 280 Gm. is allowed to pull on the end of the table). This was done by dividing the complex amplitude by the number of centimeters the baseline actually moved with the weight. Both pickups are sufficiently linear to make this correction permissible. The fluid pressure gage, which is also linear in its deflection, was standardized with three different pressures after each experiment. The standardization factor was used to calculate the femoral pressure.

Femoral arterial blood samples were obtained through the needle used for the injection. A specimen was taken before and immediately following the completion of the infusion. Venous blood specimens were taken from the femoral vein and venous pressures recorded directly by a saline manometer. All samples were then analyzed for oxygen and carbon dioxide by the VanSlyke method.

Results

The changes in heart rate and minute volume after intra-arterial histamine are summarized in table 1. It can be seen that 10 to 20 minutes after the infusion was started the heart rate had increased significantly in three of the patients, and only slightly in three. The cardiac output increased by 20 per cent or more in five of the patients within the first 20 minutes after the histamine was begun, and by only 13.8 per cent in the other subject. The changes after the infusion was stopped are shown. In general, the values returned rather rapidly toward normal. Figure 4 shows the changes in cardiac index (liters per minute per square meter of body surface) in six experiments (five patients) during the course of the intra-arterial histamine injection. The peak cardiac output

TABLE 1.—*Changes in Heart Rate and Minute Volume after Histamine*

Subject	% Change in Heart Rate *Minutes after Histamine Begun*							% Change in Cardiac Output *(cc./min.) Minutes after Histamine*					
	5	10	20	25	30	10 after finish	15 after finish	5 after begun	10	20	25	5 after finish	10
H. F. I		+8.9		+6.4	+4.5	−12.9			+4.7	+13.8		−7.1	−7.6
H. F. II		+25	+27.8			0	+4.1		+55	+54.6			−.39
F. L.		+20	+18.8			+12.5			+34.6	+41.4		+31.8	
A. W.		+22.6		+17.1		−5.5			+24.2		+25.2	−5.5	
G. B.	+12.6	+7.4	+16.8			−4.2		+38.8	+11.1	+27.0		−1.4	
C. A.	+1.2	+3.5	+10.9			−4.5		0	+16.2	+21.8		−4.0	

is reached between 10 and 20 minutes after the injection is begun. The return of the cardiac index to normal is relatively rapid; sometimes the fall occurs before the histamine is finished. Sample records from one patient (H.F.) during the second experiment for which he was the subject are shown in figure 5. The marked reciprocal changes in ballistocardiogram amplitude and femoral arterial pressure can be seen easily.

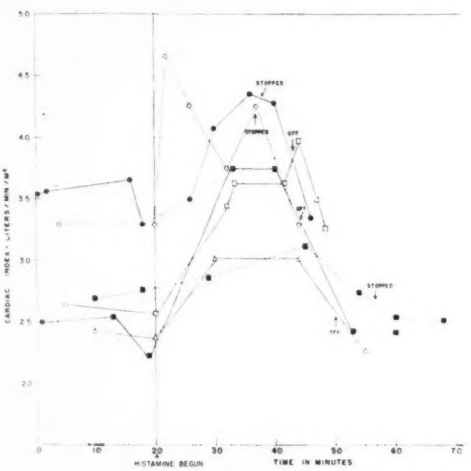

FIG. 4. Increase in cardiac index during intra-arterial histamine injection.

The femoral blood pressure changes are summarized in table 2. Both the systolic and diastolic pressures dropped in these three patients, but had risen somewhat again within 10 minutes after the infusion was stopped. The systolic pressure decreased more than the diastolic. Changes in the indirect brachial pressure were relatively slight but in the same direction as the direct femoral pressures.

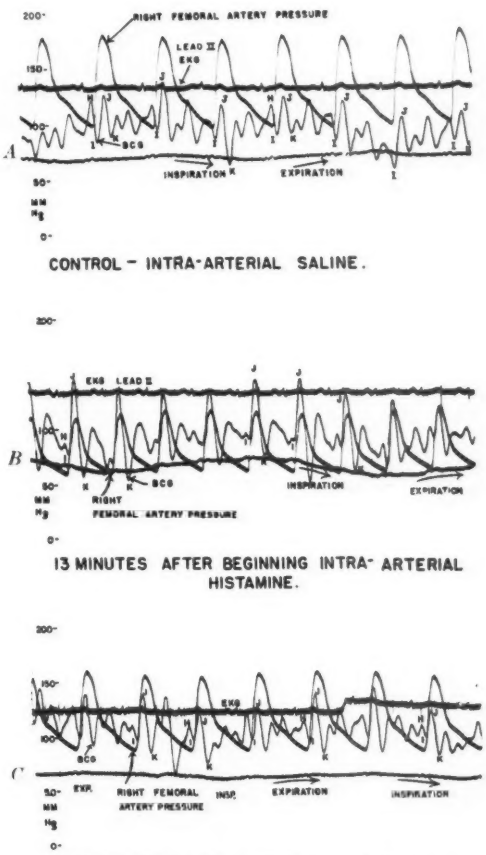

FIG. 5. Patient H. F. *A*. Control records with saline prior to histamine injection. The scale at the left is arterial pressure in mm. Hg. *B*. Marked fall in blood pressure, increase in amplitude of IJ stroke and heart rate with histamine. Note that the IJ strokes are much greater during inspiration than expiration. *C*. The record again resembles the control taken 10 minutes following cessation of histamine injection.

TABLE 2.—*Effect of Intra-Arterial Histamine on Femoral Arterial Pressure*

Subject	Direct Femoral Arterial Pressure mm. Hg					
	Control	Minutes after Histamine Begun			After Histamine Stopped	
		10	15	20	5	10
A. L.	151/63					
	149/65	134/59	130/60	137/60	140/62	144/64
H. F.	181/94	157/84	104/55	115/75	120/70	154/83
A. W.	157/72	123/61	120/62	123/61	153/81	156/80

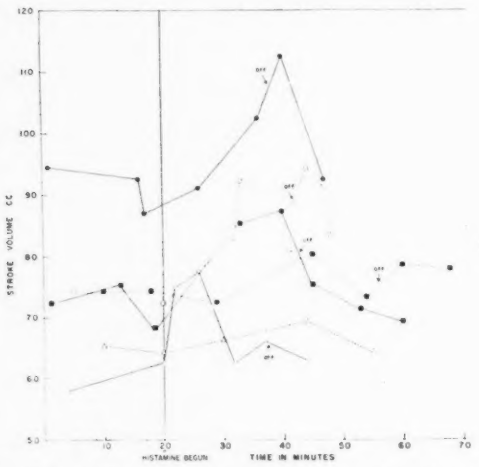

FIG. 6. This shows the changes in stroke volume during intra-arterial histamine injection in six subjects.

The stroke volume usually increased during the injection period. Four of the six patients showed a definite rise in stroke volume 15 to 20 minutes after the histamine was started. One showed only a slight increase, and the sixth patient showed no change. These data are shown in figure 6.

The effects of venous occlusion of the injected and the uninjected leg were somewhat variable. This is difficult to evaluate because the changes produced by intra-arterial histamine may be evanescent and a fall in the cardiac index apparently produced by the cuff may be the naturally occurring fall in output due to inactivation of the histamine. Table 3 summarizes the findings with venous occlusion. There is a tendency for the heart rate and cardiac output to decrease when the cuff is applied to the injected leg. This occurred in two of the patients, and, in the third, the minute volume was probably rising when the cuff was applied to the uninjected leg, since the output rose even higher after the last value recorded here. In only one patient did the output fall when the cuff was placed on the uninjected leg. Since the effects of histamine vary from one injection to the next in the same subject (table 1, H.F.) it will require further carefully planned experiments to be certain about the relationship of venous occlusion to the minute volume and heart rate. However, it does appear that these determinations rapidly revert toward normal when the cuff is applied to the injected leg.

The results in the 23 year old man with no evidence of cardiovascular disease are summarized in figure 7. This experiment was done mainly to determine if saline injection intra-arterially would cause the changes we had

TABLE 3.—*Effect of Venous Occlusion of Injected Leg*

	Cuff Applied to Injected Leg				Cuff Applied to Other Leg			
	Before		During		Before		During	
	Heart Rate Beats/min.	Min. Vol. cc./min.	HR Beats/min.	MV cc./min.	HR	MV	HR	MV
A. W.	85.5	5940	82	5200	82	5200	86	5320
C. A.	85.7	7780	86.5	7770	87.5	9035	91	9520
C. W.	91	8070	64.2	6302	74.8	6900	59.25	6480

observed. This single experiment showed some decrease in cardiac index, stroke volume, and pulse rate with saline, a change that could be due to prolonged rest in the supine position. Marked increments in cardiac index, pulse rate and a brief fall in stroke volume occurred after the histamine was begun. This subject also showed definite decrease in minute volume

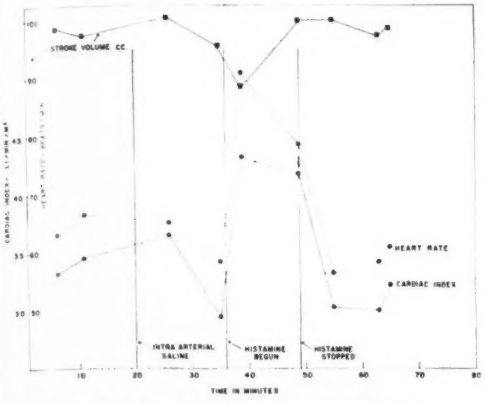

FIG. 7. Results of studies on a normal young man showing a slight decrease in pulse rate, stroke volume and cardiac index with intra-arterial saline; marked increase in pulse rate, stroke volume and cardiac index with histamine intra-arterially.

one venous sample (G.B.) which did not show these changes was drawn 15 minutes after the histamine was stopped and probably reflects the rapid return to normal of the cardiovascular adjustments.

The femoral venous pressure rose an average of 25 mm. of saline in three of the patients and was unchanged in two.

DISCUSSION

During an arterial infusion of 3 mg. of histamine diphosphate in 500 cc. of saline given over a one-half hour period into one of the femoral arteries of patients with occlusive peripheral arterial disease, the following changes have been observed in most of the subjects: (1) an increase in heart rate; (2) an increase in stroke volume; (3) a marked increase in cardiac output; (4) a fall in systolic and diastolic blood pressures as recorded directly from the femoral artery; (5) a rise in skin temperature; (6) a variable rise in femoral venous pressure; (7) an increase in oxygen saturation and a decreased carbon dioxide content of femoral venous blood; and (8) a constantly occurring fall of varying magnitude in femoral arterial oxygen saturation with slight change in carbon dioxide content.

TABLE 4.—*Effect of Injection on Femoral Arterial and Venous Oxygen and Carbon Dioxide Saturation*

Patient	Preinjection artery		Postinjection artery		Preinjection vein			Postinjection vein		
	% O_2 saturation	CO_2 vol. %	% O_2 saturation	CO_2 vol. %	Venous pressure mm. saline	% O_2 saturation	CO_2 vol. %	Venous pressure mm. saline	% O_2 saturation	CO_2 vol. %
C. A.	93	53	91.8	51	55	68.6	55.9	80	79.4	51
G. B.	90.7	47.5	83.1	49.09	72	72.9	52.9	71	71.5	52.5
F. L.	88.9	48.5	83.4	48.7	74	65	52.9	78	72.8	49.6
S. B.	91.3	48.8	89.46	48.7	56	77.6	51.8	88	86.3	47.7
H. F.	94.6	42.25	91.7	43.3	48	76.8	49.3	88	88.4	44.5

when the venous return from the injected leg was occluded, and a much smaller change when the cuff was on the other leg (table 3, C.W.).

It should be mentioned that the ballistocardiogram showed qualitative as well as quantitative changes. The pattern usually became slightly irregular with histamine, even without marked tachycardia. The respiratory variation usually increased after histamine. This is to be expected, since the respiratory variation usually increases when the cardiac output rises.

The results of the femoral arterial and venous oxygen determinations appear in table 4. The venous blood showed a definite and uniform rise in oxygen saturation and a fall in carbon dioxide. The arterial blood showed a variable fall in oxygen saturation, with the carbon dioxide changing relatively less. The

Although this series of experiments is small, we feel that these observations are worth reporting and should add to the understanding of the effects of intra-arterial histamine. The number of observations is insufficient to submit to statistical analysis; however, according to recent work establishing normal standards for cardiac output, using Tanner's formula,[11, 12] our cardiac indexes are within the proper range and the changes observed are probably

significant. The results were confirmable and relatively uniform from one subject to the next.

In order to be of lasting benefit in occlusive peripheral arterial disease, a therapeutic agent must be capable of producing an augmentation of collateral circulation to the involved extremity. In this series the majority of patients treated with intra-arterial histamine showed a definite increase in walking tolerance. The difference in physiologic effects obtained with intravenous and intra-arterial histamine is evident. This suggests that the local intensive effect of intra-arterial administration on the vascular bed of the extremity injected produces an alteration in circulatory dynamics which is quite distinct from that noted with the intravenously administered drug. One is impressed by the resemblance between the physiologic effects of intra-arterial histamine and the alterations noted in experimental and clinical arteriovenous fistulas. The tachycardia, increased cardiac output and stroke volume, fall in local arterial blood pressure, increase in local venous pressure, increase in local venous oxygen saturation and fall in local venous carbon dioxide content all suggest a shunting of blood in considerable quantity from the femoral arterial to the femoral venous circuit. Starr has previously reported a high cardiac output in a case of arteriovenous fistula as measured by the ballistocardiogram and showed a 17 per cent drop in cardiac output when a cuff was placed on the leg and inflated.[13] It was with this in mind that the occlusion cuff experiments were done. Though not conclusive, due to the factors previously discussed, the result in two of three cases showed a distinct fall in cardiac output and a slowing of the pulse rate when the blood flow to the injected leg was occluded. It is known that arteriovenous shunts stimulate the development of extensive collateral circulation, and the mechanisms of this effect have recently been reviewed.[14] In general, the larger the shunt and the longer the duration of its action, the greater is the development of the collateral circulation. However, changes of a lesser nature undoubtedly occur very early following the establishment of the fistula.[15]

Anatomic arteriovenous shunts have been demonstrated in many parts of the body.[16] The skin, muscle, liver, omentum and lungs all have been shown to possess such vessels in great numbers. Those in the lungs are of considerable size, being reported as large as 150 to 300 microns in diameter.[17] Under ordinary circumstances these vessels remain relatively contracted and of constant diameter. In response to heat, trauma or histamine marked dilatation has been reported.[18, 19] The possibility exists that the actions of intra-arterial histamine noted might be due to the dilatation of arteriovenous shunts in the leg and that the increase in walking tolerance noted is a reflection of increased collateral circulation stimulated by repeated periods of shunting. The fall in arterial oxygen saturation noted was an entirely unexpected finding and might possibly indicate shunting of blood in the pulmonary circuit. Both of these possibilities will certainly require further investigation.

Clinically, the arteriosclerotic patient with early claudication who showed a diffuse pink erythema on injection seemed to gain the most benefit from this form of injection. In considerably over 200 injections no serious complication incident to arterial puncture was encountered. No untoward systemic reactions have been noted, although our patients include one with asthma, a man with severe angina, and several individuals with borderline cardiac reserve. The transitory initial ischemia produced during the injection was not felt to be harmful and the beneficial effects obtained were thought to be due to stimulus to collateral circulation during periods of arteriovenous shunting rather than to the opening of the arteriovenous shunts per se.

Certainly no definite conclusions can be reached regarding the efficacy of this method of treatment on the basis of such a small series of cases followed over a relatively short period of time. This preliminary investigation does seem to indicate that intra-arterial histamine may have a limited field of therapeutic usefulness in selected cases of occlusive arterial disease in a class of patient that has been regarded as refractory to treatment.

Summary

1. Seven men with occlusive peripheral arterial disease were given a course of arterial infusions of histamine diphosphate. Five of the seven had good results from the course of treatment, one a fair result and one a poor result.

2. The results were measured by subjective change and objective increment in tolerance to walking on a treadmill. Those who were helped generally showed improvement by the sixth injection.

3. During the arterial infusion of histamine the following changes occurred in most of the subjects: increase in heart rate, stroke volume, cardiac output, skin temperature, oxygen saturation in the femoral vein, decrease in the blood pressure and oxygen saturation in the injected artery and arteriovenous oxygen difference, with less change in the brachial indirect blood pressure.

4. The similarity of the observed physiologic changes to those seen in arteriovenous shunts is noted.

5. It is speculated that the beneficial effects of intra-arterial histamine may be due to development of acute arteriovenous shunting and subsequent improvement in the collateral arterial circulation to the involved extremity.

Acknowledgments

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Endarteriectomy, or Surgical Restoration of the Lumen of an Obstructed Artery in Arteriosclerosis Obliterans

A Preliminary Report

By A. Núñez Núñez, M.D., B. Milanés, M.D., and J. Rodriguez Iñigo, M.D.

Endarteriectomy is an operation originally proposed by Dos Santos in which a thrombus and the portion of the arterial wall to which it is attached are removed and the lumen of the artery re-established. The technic of this operation is described. Case histories of several patients illustrating the results which the authors have obtained are presented.

ENDARTERIECTOMY or the restoration of the lumen of an obstructed artery consists in the excision of a fixed thrombus together with the portion of the intima of the artery to which it is attached. In 1946 Dos Santos[1] reported a case of thrombosis of the subclavian artery, in which endarteriectomy was performed with success, thus proving the possibility of permanent surgical recanalization of an artery, aided by anticoagulants. Later observations by Leriche,[2–4] Bazy,[5–8] Huguier[9] and Reboul[10] proved the technic to be sound.

According to Dos Santos it is dangerous to underestimate the importance of this method by considering it as a mere removal of the obstruction in a canal. All cases should be completely observed, followed up and controlled by means of arteriography to demonstrate clearly the success of the operation.

Fundamentals of Endarteriectomy

This new technic is based on anatomic, physiologic and pathologic considerations.[11]

Anatomic Basis. The existence of a plane of cleavage between the endothelium and tunica media of arteries is the anatomic basis of endarteriectomy.

The separation of the endothelium from the subendothelium of arteries is strictly histologic, since no macroscopic differentiation is possible. Together, they comprise the tunica intima or endarterial layer. Frequently the terms tunica intima, endartery and endothelium are employed without distinction.

There is a false plane of cleavage between the endothelium and the clot, but the true and best cleavage planes may be found (1) at the tunica intima, (2) in the subendothelium, (3) between the tunica intima and the elastica interna and (4) beyond the elastica interna, in the tunica media. (See fig. 1, after Arnulf.)

Physiologic Basis. Many factors play a role in the very complex mechanism of blood coagulation. In accordance with accepted facts, three factors are considered to contribute to intravascular coagulation: (1) slowing of circulation, (2) increased tendency to clotting and (3) injury to the intima.

When endarteriectomy is performed, the new canal through which the blood runs has a rough surface, thus favoring thrombus formation, but experience has shown that the blood continues to flow without clotting, provided that sufficient anticoagulant substances, such as heparin and dicumarol, are administered.

Pathologic Basis. Arteritis usually begins, from an anatomicopathologic point of view, at the tunica intima, regardless of the etiologic agent. It generally begins to affect this inner coat, except in Monckeberg's arteriosclerosis, where the tunica media is the one undergoing change. The arterial lesion, beginning in the intima, passes through several stages from proliferation through fibrosis, mucoid, hyalin

From the Section of Vascular Surgery of the University Hospital, Havana, Cuba

and lipid degeneration to atheromatosis, calcification and real ossification. These lesions produce arterial obliteration with thrombosis, forming what Bazy called a sequestrum. It is a necrobiosis formed by the clot and the intima, and is easy to remove from the rest of the arterial wall.

Indications

Dos Santos is of the opinion that endarteriectomy is indicated in cases of arterial thrombosis associated with the following conditions: (1) arteriosclerosis obliterans; (2) early endarteritis; (3) organized embolism; (4) thrombosis produced by scalenus anticus or costal compression; and (5) thrombosis caused by aneurysm.

The state of the arterial coat, as well as the plane of cleavage, are quite different in each of these conditions.

Selection of Cases

Once the clinical and arteriographic diagnoses are made, it is necessary to bear in mind several facts in order to decide whether the patient is a good surgical risk and the operation possible. Operative risk increases with the age or general deterioration of the patient. Previous heart disease, such as coronary thrombosis, and diabetes make the prognosis poor.

The operation may be considered in those cases having functional or ischemic disturbances, especially intermittent claudication. It should also be considered when organic disturbances such a necrotic ulcer or localized gangrene have occurred. Localization of the site and extension of an obstruction may be verified by arteriography.

It is necessary to study the whole length of the affected artery and its branches. This is effected by means of various arteriographic studies for the purpose of checking the patency of the distal segments, as well as the existence of other obliterated segments. These data must be considered, for they influence the anatomic and functional postoperative results.

The ideal indication is in arteritis of large vessels, especially when occlusion or marked narrowing is limited and the segment distal to the obliterated zone is patent. When thrombosis involves a long segment of an artery, the operation may be performed, but a complete restitution of flow will probably not be obtained as a result. However, an improved circulation through the vessels of the limb will be brought about by the opening up of many collateral arteries, since these tend to keep their patency for a longer time than the main trunks.

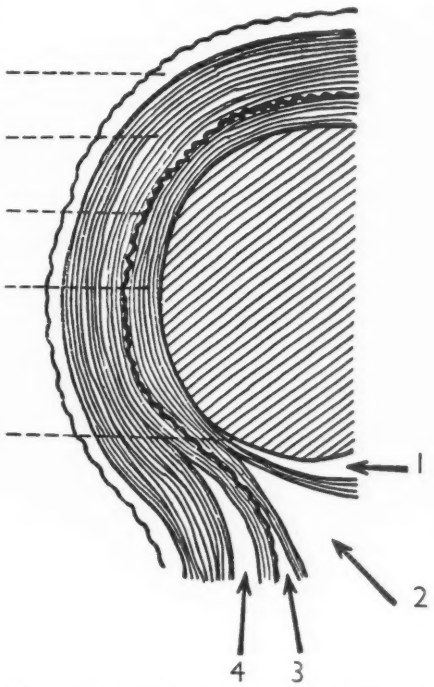

Fig. 1. Planes of cleavage in endarteriectomy (after Arnulf).

The extent of the arterial lesion is also of great importance. The most favorable results are obtained by operating on arteries whose walls are still soft and elastic, rather than on those whose walls are hardened by calcium or atheromatous infiltration.

Anesthesia

A choice may be made from the types of anesthesia that produce sympathetic block, such as, spinal or epidural for the lower extremity, or brachial plexus block for the upper extremity. The general condition of the patient

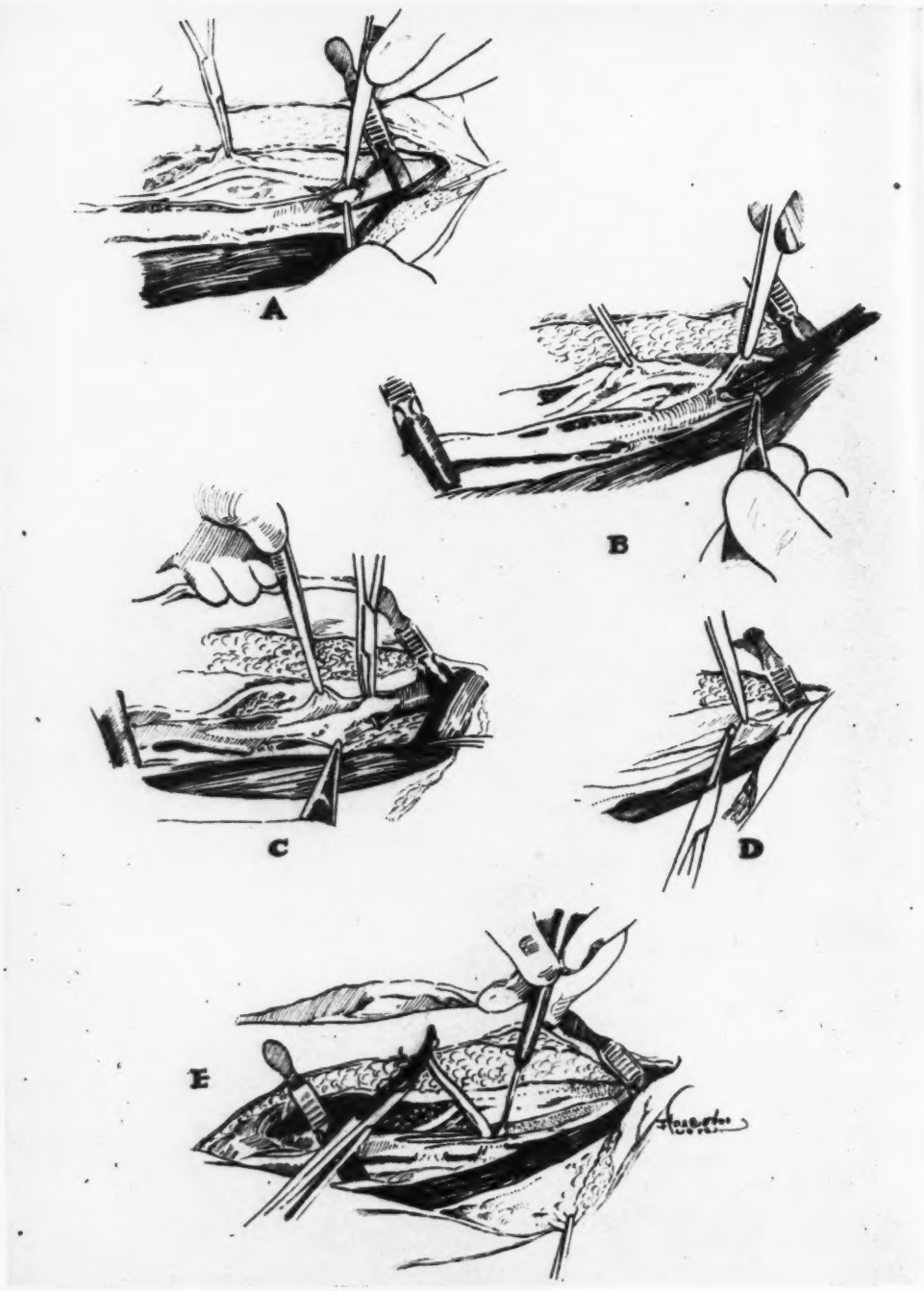

FIG. 2. Illustration of the technic in endarteriectomy. *A*. The artery has been exposed and the arterial wall is opened until the intima is prolapsed. *B*. The anterior incision is continued until the obliterated zone is passed. *C*. Circumferential dissection of the thrombus with the adhering intima. *D*. Transverse section. *E*. Excision of the thrombus and intima.

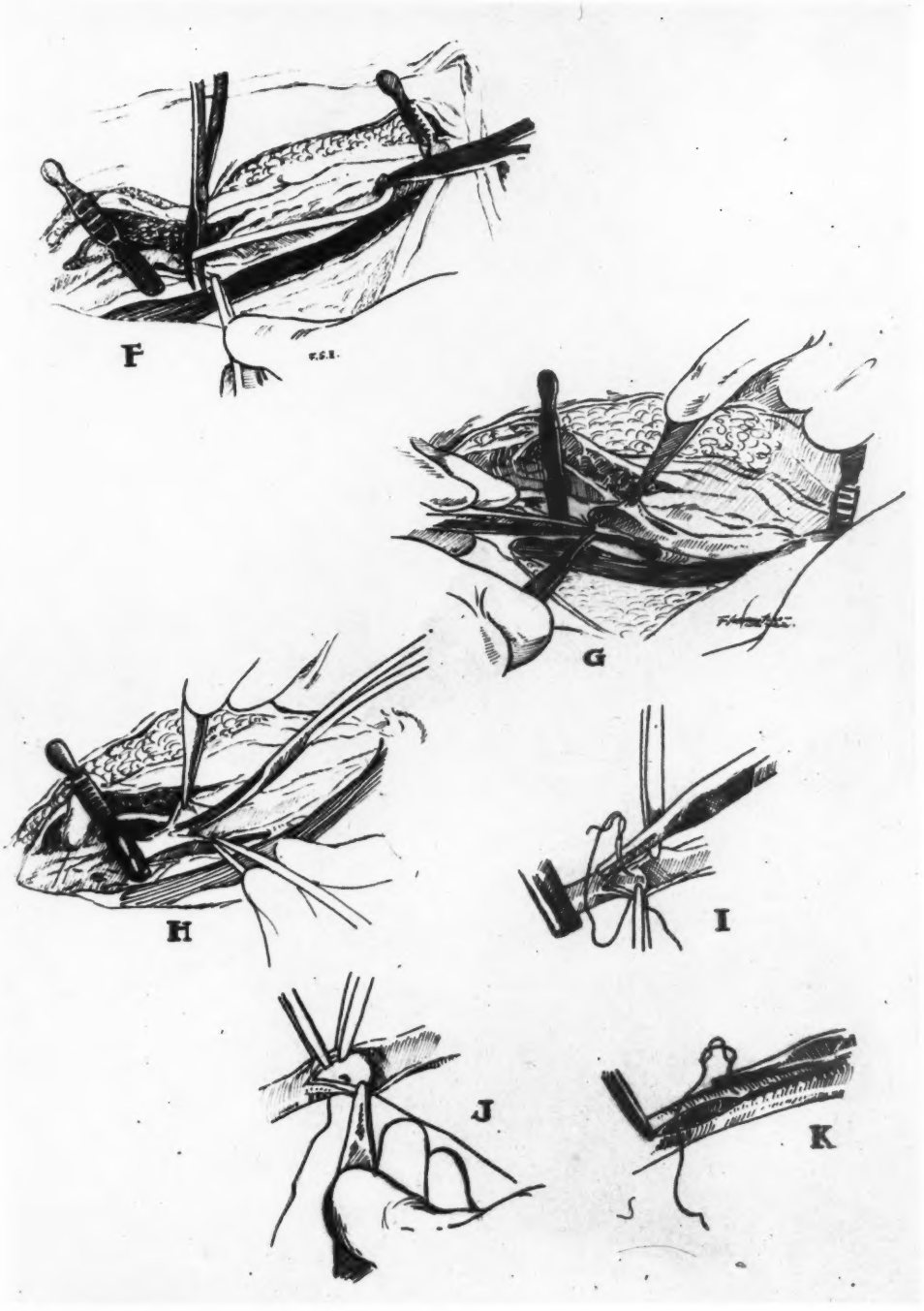

FIG. 3. Illustration of the technic in endarteriectomy (continued): *F*. Complete extirpation of the obliterated zone. *G*. Aspect of the arterial wall after elimination of the thrombosed zone. *H*. Longitudinal incision of the intima in the permeable zone. *I* and *J*. Fixation sutures of the intima. *K*. Suture of the arterial wall.

should determine the choice of the anesthetic to be used.

Operative Technic (Figs. 2 and 3)

The patient's position, the incision and the exposure of the vessel will vary in accordance with the location of the obstructed artery. Once the artery is exposed, the extent of the thrombus is determined by palpation or by puncture. The vessel should be freed one inch beyond the proximal and distal ends of the obliterated segment. Temporary hemostasis should be effected by proper clamping of the main artery proximally or distally to the thrombus and of any important collateral arteries.

An incision is made in the arterial wall following its longitudinal axis by Reboul's (continuous) or Dos Santos' (interrupted) method. We have used the former because of its advantages in the search for the plane of cleavage. We make a small longitudinal incision (fig. 2*A*) in the arterial wall 1 or 1.5 cm. above the proximal end of the thrombus. A prolapse of the intima is produced between the edges of the incision.

This incision is kept open by holding the edges with toothless tissue forceps, and, with the help of thin pointed scissors (fig. 2*B*) introduced between the prolapsed intima and the rest of the arterial wall, the intima and media are separated for a distance of 1 to 2 cm. and the overlying arterial wall is then incised. This procedure is repeated to a point 2 or 3 cm. below the distal end of the thrombus.

The intima is then dissected in its total circumference (fig. 2*C*) at its proximal end. It is cut transversely (*D*) and the thrombus is liberated with slight traction, and by the use of a thin curet the thrombus is scraped off (*E*) together with the coat formed around it by the endothelium. This is done as far as 2 cm. beyond the distal end of the thrombosed segment. A transverse section (fig. 3*F*) is made at this point in order to eliminate the whole obliterated zone. The artery, thus freed from obstruction, looks flattened and has some transverse striae (*G*) probably produced by the muscle fibers. Collateral arteries may bleed and hemostasis by clamp may again be necessary. The intima is then cut longitudinally (*H*) all the way to the end of the incision in the artery and sutured to the other layers of the artery wall by means of Kunlin[12] sutures (*I* and *J*) in order to prevent thrombosis or obstruction which develops if the cuffs of intima are left free in the blood stream.

The artery is closed (*K*) with a running suture which may be interrupted at several spots. One or 2 cm. before reaching the end of the suture, the proximal clip is taken off. The blood will flow by its own pressure, carrying out the endothelial particles that may be left. After replacing the upper clamp the suture is finished, the artery being previously washed with the heparin solution. Clamps are removed, and if there is bleeding at the site of the sutures, hemostasis is usually obtained by temporary compression. If not, additional sutures are applied. The wound is closed in layers.

Throughout the operation we continue lavage of the artery with a solution composed of 1000 cc. of normal saline solution, 1 million units of penicillin, 1 Gm. of streptomycin, 5 Gm. of Novocain or procaine and 100 mg. of heparin.

Postoperative Measures

The most important factor in the postoperative course is the administration of anticoagulants during the first seven days to prevent secondary thrombosis. This favors the formation of new endothelium. We have used the following plan: heparin is given intravenously during the first 24 hours in doses of 50 mg. every four hours. We do not test the clotting time. As soon as the patient leaves the operating room, he is given 200 or 300 mg. of dicumarol; further administration of dicumarol depends on prothrombin time. To prevent the wound from oozing, the patient's feet should be kept at a slightly higher level than the rest of the body. Extreme temperatures should be avoided because of the vasoconstrictor effect of cold and the increased tissue metabolism which results from heat.

Complications

The complications which have been reported after endarteriectomy are:

(1) Hemorrhage at the site of operation. Arnulf[11] has reported several instances of large hematomas, secondary operation having been necessary to evacuate them. These hemorrhages are due either to the rupture of the arterial suture or to the use of anticoagulants.

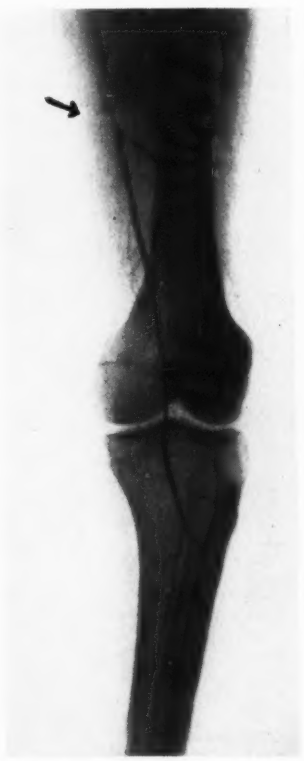

FIG. 4. Arteriography of the femoral artery in case 1 shows diminution of caliber in its medial part with the typical notching of arteriosclerosis.

(2) Secondary thrombosis. Sometimes a blood clot larger than the first one is formed, despite anticoagulant therapy.

(3) Aneurysms. The arterial wall may dilate as a result of its thinness after curettage.

RESULTS AFTER ENDARTERIECTOMY

The possibility of maintaining the patency of an artery is a proved fact. Dos Santos' patient still has a pulsating artery after three years.

Arnulf[11] states that Champy's observation of the anatomic state of the restored segment is of the greatest interest. He has reported a case in which a histopathologic study of a previously operated artery was made. It was seen that the endothelium, starting from the proximal and distal ends and from the opening

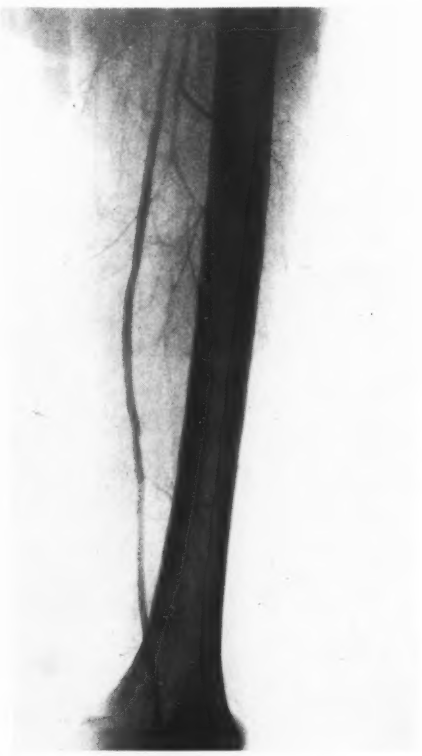

FIG. 5. Arteriography of the femoral artery in case 1 two months after operation, showing complete permeability of the arterial lumen.

of the collateral arteries, had regenerated. It is a curious fact that white blood cells form a layer that covers the inner surface. This pseudoepithelial leukocyte wall prevents the formation of a clot inside the new vessel.

When complete patency is achieved, the results are amazing; the pulse reappears, pain and coldness disappear and trophic lesions heal. Even when only partial patency is brought about, an evident functional improvement is obtained, since there is better blood circulation due to the liberation of many collateral

arteries, the periarterial sympathectomy, and the eradication of the reflex effects.

It is not yet possible for us to evaluate the latest results. Arnulf[11] states that, "Observations on endarteriectomy are still very recent. Its technic will undoubtedly be modified but its first results are of undeniably dogmatic value. The path opened by Dos Santos seems to be full of promise and to lead to a new and attractive field in vascular surgery."

FIG. 6. Aortography by the method of Dos Santos showing complete occlusion of both iliac arteries and diminution of caliber of the terminal aorta in case 2.

REPORT OF CASES

Case 1. M. P. C., a 46 year old Negro man, was admitted to the University Hospital with a history of intermittent claudication, numbness of the toes, coldness and cramps in the right calf of two years' duration. On the dorsal surface of the big toe there was a necrotic ulcer 0.5 cm. in diameter. Arterial pulse was present in the femoral artery but absent in the popliteal, posterior tibial and dorsalis pedis arteries. Slight cyanosis of the toes was observed. Oscillometric readings of the right limb showed 1 at thigh, 0 at leg and 0 at foot. Arteriography (fig. 4) demonstrated decreased caliber of femoral artery and typical notching of arteriosclerosis.

Endarteriectomy was performed on Jan. 24, 1950. A thrombus 15 cm. long was excised. Microscopic section revealed an organized coagulum with fragments of intima. Heparin was administered during the first 24 hours and thereafter dicumarol, controlled by daily prothrombin time determinations. The immediate postoperative result was the reappearance of arterial pulse in the posterior tibial and dorsalis pedis arteries.

Arteriography (fig. 5) on March 11, 1950 showed complete patency of the femoral artery. At the present time all previous symptoms and signs have disappeared, and pulse is present at the femoral, popliteal, posterior tibial and dorsalis pedis arteries.

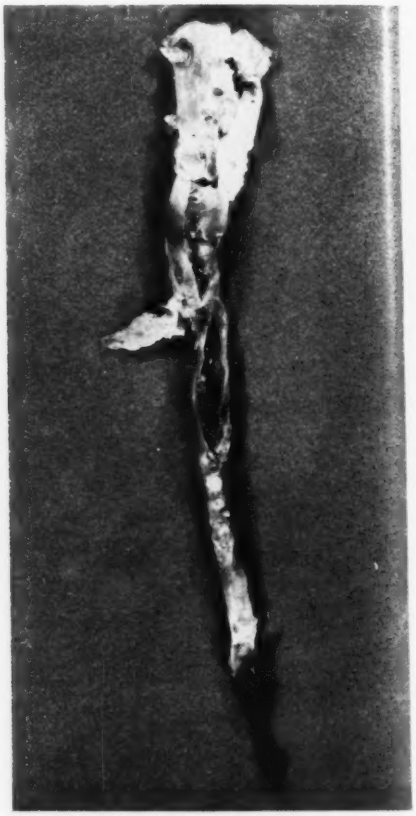

FIG. 7. Extirpated specimen in case 2. Note the thrombus covered by the intima in the terminal portion of the aorta and in the left iliac artery.

Oscillometric readings are now as follows: thigh 2; leg 1.5; and foot 1.

Case 2. S. G., a 53 year old white man, was admitted to the University Hospital with the following history: Two and a half years before admission he had felt a sudden pain in the right iliac fossa, accompanied by nausea, vomiting and coldness of the right leg. Gangrene, which soon appeared, necessitated the amputation of the leg at the middle third of the thigh. Three months later, he began to feel pain, coldness of the fingers and numbness of his

left hand, which became progressively paler. In November, 1949, he underwent another episode, with pain in the left leg, together with coldness and numbness followed by intermittent claudication, absence of pain in the whole left leg and decrease of temperature. Oscillometric readings were 0 from the femoral artery down. Aortography (fig. 6) revealed diminished caliber of the terminal portion of the aorta and complete obstruction of both common iliac arteries. Arteriographic studies were made in the femoral artery in the direction of, and also contrary to, the blood stream, thus determining the exact location of the thrombus and patency of the segment distal to the thrombosed zone.

FIG. 8. Arteriography of case 3, in which may be noted the complete occlusion of the femoral artery in its middle third with typical notchings of arteriosclerosis. Various collateral arteries supply blood to the posterior tibial artery.

Endarteriectomy was performed on Jan. 26, 1950. A thrombus, together with the tunica intima, was removed from the terminal portion of the aorta and both common iliac arteries (fig. 7). Histologic study of the removed specimen revealed crystals of cholesterol, hyalinized clots, fragments of intima, atheroma and elastoid intima.

Postoperative course: Heparin and dicumarol were administered after the scheme outlined in case 1. The pulse at femoral, popliteal, and posterior tibial arteries reappeared and the temperature of the limb increased. The patient died five days after operation.

Necropsy showed a large retroperitoneal hematoma and massive atelectasis of left lung caused by blood clots in the bronchi. Prothrombin time one hour prior the death was 20 per cent of normal. Clotting time was normal. This suggests that death was due to pulmonary embolism and retroperitoneal hemorrhage caused by a small leakage at the line of suture in the artery.

FIG. 9. Postoperative arteriography of case 3 in which may be observed the complete occlusion of the principal trunk of the femoral artery and the notable increase in the number of collateral arterial branches.

Case 3. J. V. Y., a 65 year old white man, was admitted to the University Hospital, March 16, 1950. His previous history revealed intermittent claudication and coldness of the left leg of three years' duration with gangrene of the second and third toes which necessitated amputation.

On admission he had intermittent claudication

and coldness and burning pain in a necrotic ulcer at the stump of the amputated third toe. The femoral pulse was present, but no popliteal, posterior tibial and dorsalis pedis arterial pulses were found. Oscillometric readings were: thigh, upper third, 3; thigh, middle third, 3; thigh, lower third, ½; leg, 0; and foot, 0.

Arteriographic study showed a complete obstruction of the femoral artery in its middle third with typical arteriosclerotic lesions (fig. 8). Several collateral arteries supplied the posterior tibial artery. Obliteration of the posterior tibial artery above the internal malleolus was also observed.

FIG. 10. Arteriography in case 4 with reduction of the caliber of the femoral artery in its upper and middle third with the typical notches of arteriosclerosis.

Endarteriectomy was performed on March 29, 1950, and a thrombus 30 cm. long was excised. Under the microscope, segments of the muscular and elastic coats, thickened intima and organized coagulum were observed.

Postoperative course: Heparin and dicumarol were used. The pulses of the popliteal, posterior tibial and dorsalis pedis arteries have not returned. A rise in temperature of the limb was observed. Pain disappeared from the ulcer which healed in four weeks. Oscillometric readings: thigh, upper third, 3; thigh, middle third, 3; thigh, lower third, ½; foot, 0. Postoperative arteriography showed the main trunk of the femoral artery to be occluded, but there was a noticeable increase in the number of collateral branches (fig. 9).

Case 4. U. A. T., a 60 year old white man, was admitted to the University Hospital, April 3, 1950. Two months before he had felt rest pain in the left foot and also intermittent claudication in the left leg which made it impossible for him to walk one block. Physical examination revealed a decrease in temperature of the leg and in the amplitude of the femoral pulse, with absence of pulse from the posterior tibial, popliteal and dorsalis pedis arteries. Arteriographic study showed diminished caliber of the femoral artery in its upper and middle third with notches typical of arteriosclerosis (fig. 10).

Endarteriectomy was performed on April 18, 1950, with excision of a thrombus 18 cm. long. Postoperative course: after reconstruction of the artery and removal of temporary hemostatic clamps, inspection and palpation showed the existence of pulse waves in the major branches immediately distal to the suture. The pulses of the posterior tibial, popliteal and dorsalis pedis arteries have not reappeared. Arteriography was not performed in this patient after surgery. At the present time, nine months after operation, all previous signs and symptoms have disappeared.

SUMMARY

1. Our patients upon whom endarteriectomy was performed are presented. In one a good anatomic result was obtained; in two good functional results were obtained; and one patient died after operation.

2. In arterial curettage, the thrombus is excised together with the endothelium and sometimes part of the muscular coats. It is impossible to determine the precise plane of cleavage during the operation.

3. The best results are obtained in arteritis of main arterial trunks, especially if the obstruction is limited in length and is accompanied by patency of the distal segments of the artery. This operation may be performed in patients with extensive lesions since it achieves noticeable improvement in the circulation of the diseased limb by reopening new arterial channels.

4. Arteriographic study is necessary to determine the exact location of the obstruction and the patency of the distal segments.

5. Anticoagulant therapy, properly used, is essential in obtaining satisfactory results.

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Cerebrovascular Thrombosis in Patients with Buerger's Disease

By HEINZ I. LIPPMANN, M.D.

Nine cases of cerebrovascular thromboangiitis obliterans were observed among 1700 cases of peripheral thromboangiitis obliterans. These, with 30 acceptable cases from the literature, are analyzed. Smoking appears to activate the disease, which is characterized by recurrences and remissions of focal cortical signs due to thrombosis of cerebral arteries and cortical granular atrophy. Of my patients, one died. Eight have been followed for 35 to 3 years, and with one exception all are ambulatory. Cessation of smoking is necessary. No other effective treatment is known.

CEREBRAL manifestations in patients with thromboangiitis obliterans are rare. In over 1700 cases of this disease followed for years by Silbert and his group, involvement of the brain was found only in 12 cases.

The impression gained from perusal of all published cases of cerebrovascular thromboangiitis obliterans is that the diagnostic criteria of cerebral manifestations in this condition need further clarification. Since Buerger's report in 1915 of a pertinent case,[1] more than 250 case reports have appeared in the medical literature. Many cases have been described in patients suffering from conditions commonly associated with arteriosclerosis and vascular diseases other than thromboangiitis obliterans.[1-19] Patients with multiple sclerosis[20a] and malignant glioma[21a] have been presented as instances of cerebral involvement in thromboangiitis obliterans. The belief that cerebral involvement in this disease is a well defined anatomicopathologic entity[2-5, 12, 17, 22-26] has led to confusion, as a result of which a variety of diseases has been described under the collective name of cerebral thromboangiitis obliterans.

Most authors state that cerebral thromboangiitis obliterans follows a progressive course uninfluenced by therapeutic procedures.[21] My experience with several patients suffering from this condition does not confirm this opinion. Until recently[27] many observers were pessimistic concerning the prognosis of peripheral thromboangiitis obliterans. Silbert,[28, 43] having followed a large number of cases over more than 25 years, maintains that peripheral thromboangiitis obliterans is arrested when the use of tobacco has been discontinued, and this view is now accepted by others.[29-31] Since smoking is the main factor which causes active peripheral thromboangiitis obliterans, it is reasonable to assume that this holds true in the cerebral form. Some of the case histories presented below illustrate this point.

Twelve clinical case reports are presented.* In nine of these cases the diagnosis of cerebral thromboangiitis obliterans can be made with reasonable certainty. One case is reported in detail.

Case 1, H. R., #35510 M.H., a Jewish male, aged 34, admitted in 1919. The patient had been a heavy cigarette smoker since early adulthood. In 1915, when he was 29 years old, he developed intermittent claudication in his left leg. Two years later, in 1917, when he was 32 years old, gangrene of the left foot developed and a high left thigh amputation was performed. In 1918, at the age of 33, he suffered a spontaneous right hemiplegia and aphasia which developed over a period of two days. After four months, his right arm regained some of its power and his speech improved. A few days before hospitalization, over a period of a few days, his speech deteriorated again to the point that he could utter only a few stereotyped words.

Examination in 1919 revealed a blood pressure of 130/80. He presented the picture of a right spastic hemiplegia, motor aphasia, right hemianesthesia, right central facial palsy and right hyper-reflexia. The left femoral and iliac pulses were absent. The right dorsalis pedis pulse was small, the posterior tibial pulse was absent, the right popliteal and femoral arteries were patent, as were the wrist

From the Peripheral Vascular and Medical Services, Montefiore Hospital, New York, N. Y.

* A table summarizing the 12 case reports will be supplied, upon request, with the reprints.

arteries. No abnormality of the carotid arteries was recorded. There were no signs indicative of arteriosclerosis. Blood Wassermann reaction was negative. The urine was free from albumin and sugar. At that time the patient gave up smoking upon medical advice and has never resumed this habit, to date. He was put under the custodial care of the hospital.

From 1919 to 1938 the clinical course was stationary. The blood pressure ranged from 120 to 140 systolic over from 75 to 80 diastolic.

In 1939 he developed a spontaneous right iliofemoral thrombophlebitis. The blood pressure for the first time was found elevated to 150/102. The electrocardiogram, except for left axis deviation, showed no abnormality. In 1940 a complete re-evaluation of his clinical status revealed some improvement in the motor power of his right arm, but unchanged findings in all other respects. The blood pressure was 140/100. Basal metabolic rate was plus 4 per cent. At this time, the diagnosis of a thrombosis of the left middle cerebral artery on the basis of Buerger's disease was entertained. The absence of any signs of arteriosclerosis for 20 years was commented upon by several observers.

From 1941 to 1947, the status was unchanged; the blood pressure stayed elevated. In 1943 the patient was discharged to an Old Age Home for permanent custodial care. In 1947 he developed a post-traumatic ulcer over the right tibia which healed with penicillin injections.

In September, 1948 re-examination by me revealed an obese male patient, 63 years of age, grey-haired, cheerful and with a youthful facial expression. He was confined to a wheel-chair on which he moved about with great agility. He understood spoken and written words and was oriented as to time and place; he answered questions with gestures. His aphasia was complete. There was no arcus senilis. The eye grounds and pupillary reactions were normal. Chest and heart, except for an accentuated second aortic sound, were normal. The abdominal organs were normal. There was a healed left, high thigh amputation stump. Both carotid arteries were patent, as were all wrist arteries. The right femoral artery was open, the right popliteal artery could not be felt, the right dorsalis pedis and anterior tibial arteries could be felt weakly pulsating, the posterior tibial artery was closed. No iliac or femoral pulse could be found on the left side. Oscillometric readings were 2.0 at the right ankle, 4.0 at the right calf, trace at the left thigh stump. There was no albumin or sugar in the urine. Blood sugar was normal. The electrocardiogram was normal. The blood pressure was 170/100 at the right and 185/105 at the left arm. Re-examination in May, 1950 revealed the same findings.

Comment

This is a 36 year follow-up of a male patient, now 66 years old, who at the age of 29 developed occlusive peripheral vascular disease resulting in gangrene of the left foot. A left thigh amputation was carried out two years later. Another two years later, when he was 34 years old, he developed a right-sided hemiplegia and motor aphasia in two episodes at a few months interval. At this point, the patient gave up smoking. Since then, namely for the past 31 years, his peripheral vascular disease and cerebral involvement have failed to manifest any progressiveness. The neurologic and peripheral vascular findings were identical in 1919 and 1950. The blood pressure was normal at the time of the hemiplegia and for 20 years thereafter. Subsequently, the patient developed essential hypertension without altering the benign clinical course for the past 11 years. The absence of detectable signs of arteriosclerosis such as an arcus senilis, tortuosity of peripheral arteries, retinal artery changes, albuminuria, and electrocardiographic changes is noteworthy. He was a heavy smoker when the disease was active. After cessation of smoking, the disease came to a standstill and has been arrested for 31 years.

In this patient, a remarkable psychologic and physical adjustment has taken place considering the widespread damage caused by active occlusive vascular disease in its initial stages.

Discussion

The name thromboangiitis obliterans, as proposed by Buerger and accepted in this country for 40 years, denotes a clinical-anatomic entity. The disease involves the large and medium-sized arteries and veins of the extremities and may involve visceral vessels. It is conceivable that thromboangiitis obliterans may start in the visceral vessels and later manifest itself in the extremities. However, in the present state of our knowledge, one cannot be certain that a disease process involving the visceral vessels alone is thromboangiitis obliterans, no matter how much it resembles the lesions in the extremities either in gross or in microscopic appearance.

When thromboangiitis obliterans is considered from the anatomic standpoint alone, the findings are not sufficient to establish the diagnosis. The lesions of the acute stage described by Buerger[32] in superficial and deep veins are rarely found in arteries.[33-36] Isolated instances of acute lesions in visceral vessels[37-39] have been described. However, lesions of identical histologic appearance are also seen in conditions other than thromboangiitis obliterans.[36, 40, 44] It has been known for a long time[41]

that, at least in part, the histologic picture of acute thromboangiitis obliterans is due to nonspecific reaction of the vessel intima.

Later stages of thromboangiitis obliterans produce anatomic lesions which are more characteristic. The signs of a subsiding inflammation, the preservation of the internal elastic membrane of the involved blood vessel together with the absence of evidence of degeneration and calcification are distinctive features of thromboangiitis obliterans past the acute stage. Nevertheless, some pathologists insist that there must be a clinical history of involvement of the extremity vessels before a diagnosis of thromboangiitis obliterans in the visceral vessels can be accepted.[42]

Thromboangiitis obliterans past the subacute stage may lead to an anatomic picture which is interpreted by most observers as arteriosclerosis superimposed upon the lesion of thromboangiitis obliterans.[45] This belief has recently been challenged by von Albertini[36] who maintains that thromboangiitis obliterans produces lesions which ultimately resemble but can be distinguished from arteriosclerosis; he furthermore contends that the transition from the picture of acute thromboangiitis obliterans to the end stages of the disease may be completed in less than two months.

From a clinical point of view, the diagnosis of thromboangiitis obliterans in a nonsmoker is open to doubt. The overwhelming experience has shown that all patients with thromboangiitis obliterans are smokers. A follow-up of 1400 cases of many years[43] has demonstrated that the disease is arrested when smoking has been discontinued, provided tissue damage has not advanced irreversibly, or has not involved vital organs.

The diagnosis of thromboangiitis obliterans should not be made in patients with conditions associated with arteriosclerosis, in patients in whom the onset of symptoms in the extremities occurs after 50 years of age, in those suffering from other arteritides and phlebitides (syphilis, tuberculosis), and in those with vascular injuries (frostbite, immersion foot). Each of these conditions can produce clinical and anatomic manifestations similar to thromboangiitis obliterans.

A low basal metabolism, high blood cholesterol, low blood volume and signs of relative concentration of the formed elements of the blood are often found in thromboangiitis obliterans.[52-54] However, in otherwise characteristic cases, the absence of any of these tests is of no significance. Special studies such as the observation of the nail fold capillaries,[51] determination of arterial and venous oxygen content and capacity,[47a, b] the heparin tolerance test,[8] to name only a few, have not proved to be helpful in arriving at a diagnosis of thromboangiitis obliterans.[49, 50]

The Diagnosis of Cerebral Thromboangiitis Obliterans

I. *Anatomy*

The anatomicopathologic lesions that are said to be characteristic of the cerebral form of the disease are cortical cerebral atrophy and encephalomalacias, thrombosis of one or more major cerebral arteries and structural changes of the cervical sympathetic chain.

According to Spatz and collaborators[25] and pupils[23, 24] cerebral thromboangiitis obliterans manifests itself in two anatomic forms: granular atrophy of the cortex in a sickle-shaped distribution and discontinuous foci of cerebral softening. The first of the two was described in cases of thromboendarteritis of the anterior, medial and posterior cerebral arteries, singly or in combination, which grossly appear wormlike and histologically reveal intimal proliferation and thrombosis. Patients suffering from this type are said[24, 25] to present various emotional disturbances such as depression, forced crying, fatigue and also aphasia. The second of the two, discontinuous cortical encephalomalacias, was described in thrombosis of the larger brain arteries. These patients are said to suffer from various forms of cortical symptoms and signs, mono- and hemiplegias, pareses and aphasia.

Re-study of the case material[2, 23, 26] on which this anatomic description is based leaves no doubt that many cases have been included which do not fulfill the criteria for the diagnosis of thromboangiitis obliterans. Even from the standpoint of descriptive anatomy and histology only, the distinctiveness of the cerebral form of the disease has been questioned by von

Albertini.[55] The same author pointed out[56] that the first anatomic description of cerebral thromboangiitis obliterans by Spatz was based on a case suffering from recurrent cerebral emboli and not thromboangiitis obliterans. Other diseases in which granular cerebral atrophy of encephalomalacias have been observed are arteriosclerosis,[57] chronic rheumatic cerebral disease,[58] chronic heart failure,[57, 61] hypertension and chronic kidney disease,[61] carbon monoxide poisoning,[60] and embolism.[55, 59]

Subendothelial bleeding into the involved cerebral artery was described as the first anatomic sign of cerebral involvement[62] but not as a distinctive feature of thromboangiitis obliterans since it is found in arteriosclerotic involvement as well.[63]

Thrombosis of the internal carotid, vertebral, medial cerebral, anterior and posterior cerebral arteries has been described in patients with thromboangiitis obliterans[56] in order of frequency. It appears to account most frequently for cerebral complications in Buerger's disease. Among 30 acceptable cases, it was encountered 21 times. It is well known that in many pathologic conditions other than thromboangiitis obliterans, thrombosis of the carotid and cerebral arteries may be found.[15c] Attempts at establishing an etiologic diagnosis have been made in such cases by means of biopsy[15] and arteriography,[15, 21] but it appears doubtful at the present time that either method has yielded findings specific for thromboangiitis obliterans.

Structural changes in the cervical sympathetic chain in thromboangiitis obliterans with cerebrovascular complications have been described.[64] This should be accepted with caution, since the interpretation of the histologic appearance of the sympathetic ganglions and perighanglionic tissue, with the available methods, has been controversial even among experienced observers.[65] Likewise, reports on structural changes of the sympathetic chain in involvement of the extremities have been contradictory.[66, 67]

In conclusion, there is no proved characteristic anatomic picture of cerebrovascular involvement in thromboangiitis obliterans. Most patients suffering from Buerger's disease who actually developed cerebral complications had thromboses of one or several cerebral arteries and some had cortical granular atrophy.

II. *Clinical Course*

Of more than 250 case reports of cerebrovascular thromboses in the literature, only 30 can be accepted as being caused by thromboangiitis obliterans, if the above-mentioned diagnostic criteria are applied. A considerable number of those that might be due to cerebral complications fail to include sufficient clinical data to establish a diagnosis. This is particularly true for some detailed anatomic,[22, 23] histologic,[26] psychiatric[68] and clinical reports[11, 25, 69, 75] on cerebral thromboangiitis obliterans. Finally, many cases reported as cerebral thromboangiitis obliterans suffered from diabetes, hypertension, chronic kidney disease and other diseases.[2-21]

The following discussion is based on 39 cases (see table 1), 30 cases from the literature and 9 of the 12 cases observed by me. In three cases of my series, the diagnosis is open to doubt.*

All cases in the literature here discussed were males, and four among the nine cases of my group were females. The relatively high incidence of cerebrovascular complication in female patients with thromboangiitis obliterans in this group was first pointed out by Silbert.[97]

Nineteen of the 30 cases from the literature and three of my nine cases, that is 22 of 39 cases (56 per cent), first developed peripheral vascular and then cerebrovascular disease within a few years. If cerebral thromboses develop when the peripheral vascular disease has been quiescent for many years, one cannot be certain of the diagnosis, since arteriosclerosis may have supervened. My cases 7 and 9, in whom cerebral thrombosis developed 20 and 27 years following peripheral thromboangiitis obliterans, have not, therefore, been included in the discussion of the clinical course.

Six of the 30 cases in the literature and six of my nine cases, that is 12 of 39 cases, first developed cerebrovascular and then peripheral vascular disease in fairly short order (see table 2). In my cases, three out of six of this last

* A table summarizing 12 case reports observed by the author will be supplied, upon request, with the reprints.

TABLE 1.—*List of Thirty Acceptable Cases of Cerebrovascular Thromboangiitis Obliterans in the Literature*

Year	Author	Case no.	Sex	Onset age PVD*	Onset age CVD†	Clinical data	Site of occlusion *italics if verified by autopsy*
1915	Buerger[1]	9	M	?	?	Incoherent speech	?
1926	Cserna[84]		M	20	35	Recurrent right hemiparesis	*Malacias in stratum subcallosum and putamen*
1927	Lewis[85]		M	40	47	Left hemiplegia	*Left common carotid, right external carotid arteries*
1928	Stahnke[86]		M	21		Died suddenly	*Left arteria fossae Sylvii*
1929	Nordmann and Reuys[87]		M	41		No cerebral symptoms	*Malacia of right temporal lobe*
1929	Barron and Lilienthal[88]	1	M	41	48	Right hemiparesis	Left middle cerebral artery
1932	Bauer and Recht[89]	1	M	38	44	Recurrent left hemiparesis	Right middle cerebral artery
1933	Foerster and Guttmann[76]	1	M	34	31	Recurrent right hemiparesis, amaurosis	Left middle cerebral artery. Left cerebral cortical atrophy
		2	M	34	26	Left hemiparesis, aphasia, migraine	*Right middle cerebral artery*
1933	Merkelbach[90]		M	31	30	Left hemianopia	?
1933	Livingston[91]		M	34	36	Died suddenly	Left middle cerebral artery.
1934	Averbuck and Silbert[92]	37	M	37	44	Hemiplegia	?
1934	Poetzl[74]	6	M	29	29	Recurrent right hemiparesis	Left middle cerebral artery
1935	Essen[93]		M	31	45	Left hemiplegia	Right middle cerebral artery.
1936	Cabot[94]		M	48	48	Dizziness	? .
1938	Hausner and Allen[10c]	2	M		44	Right hemiplegia, aphasia	Left middle cerebral artery.
		3	M	37	37	Left hemiplegia	Right middle cerebral artery.
		4	M	39		Left hemiplegia	Right middle cerebral artery.
		8	M	43	28	Right hemiparesis, aphasia	Left middle cerebral artery.
1938	Meves[4b]	1	M	40	39	Left hemianopia	?
		2	M	25	35	Recurrent facial paresis and aphasia	?
1938	Straeussler Friedmann and Scheinker[18a]	2	M	37	39	Recurrent left hemiparesis	*Left arteria fossae Sylvii*
1939	v. Hasselbach[95]	3	M	22	35	Recurrent left hemiplegia	Right middle cerebral artery
		6	M	37	37	Recurrent hemiplegia	?
		7	M	34	44	Fainting spells, migraine	?
1941	Sunder-Plassmann[21c]	3	M	40		Headaches, fatigue, visual disturbances	?
1941	Nils Antoni[12a]	2	M	36	37	Right hemiplegia, spastic quadriplegia	*Basilar and vertebral arteries*
1944	Krayenbuehl and Weber[15d]	16	M	46	46	Right hemiplegia	Left internal carotid artery
1947	Davis and Perret[16b]	11	M	53	53	Recurrent left hemiparesis	Left internal carotid artery
1948	Llavero[20d]	10	M	33	25	Recurrent dizziness on effort. Epilepsy. Right hemiplegia.	Left middle cerebral artery

* Peripheral vascular disease † Cerebrovascular disease

group (cases 4, 5 and 11) developed the arterial occlusion in the paretic limb. Patients with spastic hemiparesis are known to exhibit spastic vascular phenomena on the involved side. It has been suggested[70] that the same mechanism may lead to organic vascular occlusion in the extremities. The vascular occlusion in the extremities was of sudden onset in two of my cases and without detectable preceding vasoconstriction on the involved side. In one additional case, thrombophlebitis was observed as well. In one case (case 12) peripheral occlusion developed in the nonparetic leg, and in two other cases (cases 3 and 10) the involvement of the peripheral vessels was bilateral.

All cases of cerebral thromboangiitis obliterans described in the literature, with the exception of two where data concerning the use of tobacco are not given, were smokers. All patients in my series were smokers. The material here reported offers data which illustrate the causal relationship between smoking and disease activity in the cerebral form of thromboangiitis obliterans (cases 1, 4 and 6). Of these, one patient developed gangrene of one leg and hemiplegia in short order. Only a short time after he gave up smoking did his disease become inactive. Today, the patient reveals the same peripheral vascular and central nervous system findings as he did 31 years ago. One patient (case 4) continued to smoke after the onset of his cerebral symptoms and within a period of four years developed hemiplegia, aphasia, and peripheral arterial occlusion as well as thrombophlebitis. Another patient (case 6) alternated between several months' periods of abstinence from smoking and resumption of this habit against medical advice. During this period, he experienced the development of thrombosis of a cerebral artery, two recurrences of a brachial artery thrombosis and coronary artery thrombosis. In each instance the resumption of smoking had preceded the onset of a thrombosis by some weeks. When this patient was last examined, he had given up smoking for more than four months and his symptoms were rapidly improving.

It is generally recognized that smoking may cause constriction of the peripheral blood vessels[71] especially in patients with thromboangiitis obliterans.[72] Several reports in the literature give suggestive evidence of cerebral blood flow disturbance[73, 74] in patients with thromboangiitis obliterans who smoke.

Of the nine cases reported here, two (cases 1 and 2) stopped smoking after cerebral paresis had developed. In none of these was there a thrombotic closure of cerebral or other arteries during subsequent observation for a long time; the first of the two patients was observed for 31 years without any further disease activity. In contrast to this course in the nonsmokers, those who continued to smoke after the onset of cerebral paresis, six (cases 3, 4, 5, 10, 11 and 12) developed peripheral artery occlusions, and one (case 6) developed a thrombosis of the brachial artery in two episodes and a thrombosis of the coronary artery. This suggests that cerebral thromboangiitis obliterans remains an active disease as long as the patient smokes, although the activity is not limited to the cerebral vessels.

Of the three cases with doubtful diagnosis, cases 7 and 9 had a cerebrovascular accident 20 years and 27 years respectively after the peripheral vascular disease had become manifest. It is reasonable to suggest that arteriosclerosis

TABLE 2.—*Sequence of Cerebrovascular and Peripheral Vascular Involvement in Thromboangiitis Obliterans (Thirty-nine Cases)*

Cases	After years						Total	
	1–5		6–10		11–20			
	No.	%	No.	%	No.	%	No.	%
A. CV after PV involvement								
Literature	10	25.6	6	15.4	3	7.7	19	48.7
This series	2	5.1			1	2.6	3	7.7
B. PV after CV involvement								
Literature	3	7.7	2	5.1	1	2.6	6	15.4
This series	5	12.8	1	2.6			6	15.4
C. No data available								
Literature							5	12.8
This series							0	
Total							39	100.0

had supervened in both cases. Case 8 reveals a bizarre course suggestive of retinal artery spasm, peripheral occlusive arterial disease, transient hypertension and a cerebral thrombosis after subsidence of the hypertension. A final diagnosis is deferred in this case.

For reasons unknown, the most frequent site of cerebral arterial occlusion in patients with thromboangiitis obliterans is the left middle cerebral artery (see table 3) and its branches.

Not unlike the development of the peripheral lesions, which follow a characteristic pattern of recurrent segmental arterial closures, cerebrovascular thromboangiitis obliterans manifests itself in recurrent attacks of cortical signs such as fleeting monoplegias, hemianopia, hemiplegia and paresis, aphasia interrupted by remissions of unpredictable duration. The transient character of these initial signs of cerebral involvement has led some observers to believe that spastic phenomena account for the development of the cerebral manifestations. However, with each recurrence of the cerebral signs, more extensive and longer lasting damage can be noted. Twenty recurrences of hemiparesis were reported in one case in the literature; the attacks increased in intensity and extensiveness and climaxed in a permanent hemiplegia.[12] In my series four such attacks preceded the establishment of hemiparesis in case 4, three in case 2 and two in cases 1 and 6.

TABLE 3.—*Site of Arterial Occlusion in Cerebrovascular Thromboangiitis Obliterans (thirty cases from the literature and nine of this series*).*

	No.	%
Left middle cerebral artery	16	41
Right middle cerebral artery	9	23
Left internal carotid artery	2	5.2
Left common carotid artery	1	2.6
Right common carotid artery	1	2.6
Left and right vertebral arteries	1	2.6
Unknown	9	23
Total	39	100%

* Including the postmortem findings in seven cases of the literature. In the remaining 23 cases of the literature and the nine cases of this series, only clinical data were available to determine the site of cerebrovascular occlusion.

Even if the recurrent attacks of paresis do not continue until permanent irreversible hemiparesis results, there are clinical signs suggestive of organic rather than spastic vascular occlusion. Thus, in case 2 a transient left hemiparesis was observed which subsided after two days and never recurred, while a positive Babinski reflex of the involved side persisted for many months. Whether widespread vasospastic phenomena accompany the onset of recurrent small vascular occlusions could not be established in this series, since I did not make use of arteriography in my patients.

It is a distinctive feature of this disease that with each recurrent cerebral insult the site previously involved is damaged again. There is no dissemination of the pathologic process as found in multiple sclerosis.

Some observers mention that attacks of prostration, perspiration, dizziness, and transient visual disorders such as scotomas may precede the development of the above described focal cerebral signs and that these prodromal symptoms are entirely reversible.[12, 75] Such symptoms were not observed in any of the cases reported here.

Transient contraction of the retinal vessels, causing temporary amaurosis, has been observed[76] in patients with cerebral thromboangiitis obliterans. In the only patient in this series in whom this happened (case 8), a definite diagnosis of cerebrovascular thromboangiitis obliterans cannot be made. Sheathing of the retinal veins has been reported in patients with cerebral manifestations[69] but could not be seen in this series. Interestingly, both phenomena of retinal artery spasm and retinal vein sheathing have also been reported in patients with multiple sclerosis.[77, 78a,b] The similarity of the clinical course in both diseases has been pointed out.[75]

Apart from the occasional occurrence of a central retinal artery thrombosis in patients with thromboangiitis obliterans,[79] permanent changes of the retinal arteries are probably rare.[56] This is in keeping with the experience that thromboangiitis obliterans involves middle-sized and large rather than small arteries.[80] Older reports to the effect that thromboangiitis obliterans may and frequently does involve the retinal blood vessels[81] and may be associated

with cerebral involvement[17] are probably accounted for by a faulty interpretation of anatomic and histologic findings[82] and the selection of patients disregarding the diagnostic criteria for thromboangiitis obliterans.[83]

It has been pointed out that cerebral manifestations of this disease may lead to epilepsy and petit mal.[12, 75] Significantly, these attacks involve the limbs previously involved, paralyzed or paretic and, if jacksonian in nature, do not spread over other parts of the body. One of the cases discussed here (case 2) developed attacks of petit mal brought on by physical effort. They were stopped for 18 months when the patient avoided physical exertion. Following a long automobile trip which entailed considerable exertion, the patient had an epileptic seizure lasting for several days, followed by massive thrombosis of one femoral vein and artery with gangrene, to which she succumbed.

TABLE 4.—*Prognosis of Cerebrovascular Thromboangiitis Obliterans*

Case No.	Follow-up after onset of PVD in years	Follow-up after onset of CVD in years	Present condition
1	35	31	same as 31 years ago—wheelchair
2	12	7	died
3	17	19	working
4	4	11	working
5	5	8	working
6	14	1	unknown, last seen in 1945
7	25	3	retired, ambulatory
8	6	6	working
9	27	1	working
10	11	12	working
11	12	14	working
12	1	3	working

PROGNOSIS OF CEREBRAL THROMBOANGIITIS OBLITERANS

Seven of 30 cases described in the literature died from cerebrovascular disease. In this series of nine, one died. This corresponds to an overall lethality of 21 per cent.

Those in my series who survived have been followed over a number of years (see table 4). With the exception of one patient who did not present himself again, and one who has been confined to a wheel chair since the onset of his cerebrovascular disease, all patients are ambulatory. This would suggest that cerebral thromboangiitis obliterans does not have a grave prognosis for life and does not follow a progressive course. If the initial damage inflicted upon the brain has been extensive, the prognosis for life is altered for the worse; in the one patient of this series who succumbed, evidence of bilateral widespread brain damage was present.

TABLE 5.—*Persistence of Symptoms in Patients with Cerebrovascular Thromboangiitis Obliterans*

Patient No.	Paresis	Aphasia	Years followed	Remarks
1	unchanged	unchanged, complete	31	
2	unchanged	unchanged	7	died
3	mild, unchanged	none	19	
4	unchanged	mild, unchanged	12	
5	improved	improved	9	
6	unchanged	mild, unchanged	2	
7	improved	improved	4	on a-s base
8	improved	improved	1	doubtful CV-TAO
9	improved	improved	2	on a-s basis
10	mild, unchanged	none	12	
11	mild, unchanged	none	14	
12	mild residue	none	3	

Once hemiparesis or hemiplegia have been present for more than a few months the chances that functional recovery will take place are very slight (see table 5). Those who developed aphasia have shown not more than slight speech improvement or none at all over many years. Attempts at speech re-education in one case (case 2) have been unsuccessful.

Smoking has a deleterious effect upon the prognosis of the cerebral form of the disease since there is reason to believe that the cerebral thromboses in patients with thromboangiitis obliterans occur only when the patients smoke.

Moreover, those in my series who gave up smoking after their cerebral accident have presented no evidence of further vascular occlusion. Those who continued smoking developed thromboses in peripheral or visceral arteries. The conclusion appears justified that cerebrovascular thromboangiitis obliterans is an active disease only in smokers.

Treatment of Cerebrovascular Thromboangiitis Obliterans

Cessation of smoking is a necessity. The rationale for this has been discussed above.

Cervical sympathectomy has been performed in two cases by Foerster and Guttman[76] in 1933 and additional cases have been reported by Foerster's pupils[69] and others[21c] without notable success. I doubt that blocking of the cervical sympathetic outflow as recently voiced by DeTakats for treatment of the cerebral insult can be of help in cerebrovascular thromboangiitis obliterans. Its effect was studied in one case of this series (case 4) and exerted no effect on the neurologic signs or the electroencephalographic pattern. Likewise, the adrenergic blocking agent, Dibenamine, administered intravenously, was ineffective. Whether these procedures are of value in patients treated in the acute stage of cerebral thrombosis remains a matter of future trial. Likewise, the resection of a thrombosed artery (Leriche) and periarterial sympathectomy[15, 64] have been inconclusive.[20c]

I do not have enough experience in the use of anticoagulants as therapeutic agents in cerebrovascular thromboangiitis obliterans. They were used in one patient of this series, with no result (case 2). The use of vasodilators (e.g., papaverine) by mouth has been recommended for a long time and has been employed in several patients of this series with no untoward effects. I do not believe they were of any value. The more logical use of vasodilators administered into the carotid artery (provided it is patent) has not been tried to my knowledge. In all other respects, patients with cerebrovascular thromboangiitis obliterans ought to be treated according to the same principles as other patients with cerebrovascular thromboses.

Summary and Conclusions

Of 1700 cases of peripheral thromboangiitis obliterans studied by Silbert and his associates, only 12 with cerebrovascular involvement were encountered. A diagnosis of cerebrovascular thromboangiitis obliterans could be made in only nine of these cases. In two, superimposed cerebrovascular arteriosclerosis and in one, cerebral thrombosis of unknown origin were diagnosed. Four cases in this small series occurred in women, a relatively high incidence. The over-all incidence of cerebrovascular complications in thromboangiitis obliterans amounts to less than 0.5 per cent.

It appears from a study of the literature that cerebrovascular thromboangiitis obliterans is diagnosed too often. Diagnosis of the disease is justified only if peripheral thromboangiitis obliterans is present. The diagnosic criteria of peripheral thromboangiitis obliterans are summarized. Survey of the literature discloses that cerebrovascular involvement presents no distinctive pathologic anatomic picture. The nonspecific structural lesions most frequently encountered have been thrombosis of one or more large or medium-sized brain arteries or their branches and cortical granular atrophy.

Thirty acceptable cases of cerebrovascular thromboangiitis obliterans in the literature and nine personal cases are discussed.

Clinical data are given which suggest that smoking activates the cerebral manifestations of thromboangiitis obliterans. The clinical course is characterized by frequent recurrences and remissions of the same focal cortical signs which terminate in permanent damage. The most frequent signs are hemiparesis or hemiplegia and partial or complete aphasia.

If cerebrovascular thrombosis is seen in young people in whom rheumatic heart disease or other sources of embolic disease, hypertension, diabetes, brain tumor or multiple sclerosis have been ruled out, the diagnosis of cerebrovascular thromboangiitis obliterans should be suspected. The patient should be examined and followed-up for the presence of occlusive peripheral vascular disease. Such a patient should be forbidden to smoke.

The prognosis for life is favorable provided the initial damage to brain tissue has not been too extensive and the use of tobacco has been discontinued. Aphasia and hemiparesis tend to persist with slight or no improvement.

Apart from the cessation of smoking, there

is no known effective treatment of cerebrovascular thromboangiitis obliterans. Blocking or removal of the cervical sympathetic chain, the use of sympatholytics and anticoagulants have not proved to be beneficial. Vasodilators were innocuous but their therapeutic value in the cerebral manifestations of thromboangiitis obliterans is questionable.

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The Syndrome of Short P-R Interval, Normal QRS Complex and Paroxysmal Rapid Heart Action

By BERNARD LOWN, M.D., WILLIAM F. GANONG, M.D., AND SAMUEL A. LEVINE, M.D.

A short A-V conduction time, whether present with normal or with abnormal QRS complex, is associated with an increased incidence of paroxysmal rapid heart action. There are a considerable number of patients who have a short P-R interval, normal QRS complex and bouts of tachycardia. They are usually females, in middle life, devoid of organic heart disease and exhibit a snapping apical first heart sound. They do not demonstrate any of the features of anomalous A-V conduction. Evidence is presented suggesting the operation of endocrine and autonomic nervous system factors in the genesis both of the short P-R interval and the tachycardia.

IN 1930 Wolff, Parkinson and White[1] described a distinctive electrocardiographic pattern in certain patients with benign paroxysmal tachycardia. This pattern, now widely recognized, consists of a short P–R interval, usually less than 0.10 second in duration, and a prolonged QRS complex slurred on the upstroke. It was also observed that occasionally the P–R intervals and QRS complexes simultaneously revert to normal. This may occur either spontaneously or as a result of vagal suppression induced by atropine or exercise. The genesis of this syndrome is at present accounted for by the presumed existence of single or multiple accessory auriculoventricular conduction pathways.[2, 3] The short P–R interval is believed to be the result of the passage of the atrial impulse along such anomalous channels with a short-circuiting of the normal pathways. The altered configuration of the QRS reflects the aberrant sequence of depolarization of the ventricular myocardium. The extensive literature which now exists on this subject includes instances which, though possessing all other features of this syndrome, have P–R intervals of 0.12 second or more[4, 5] and examples with QRS complexes which, though slurred in their initial portion, are of normal duration.[6, 7]

In recent years we have been impressed by the frequent association of paroxysms of rapid heart action and short A-V conduction time in individuals with QRS complexes of normal duration and configuration. However, to date only 11 such cases have been reported.[8–14] They have usually been regarded, without adequate justification, as variants of the Wolff-Parkinson-White syndrome. The present study has the following three objectives: first, to ascertain the incidence of paroxysmal tachycardia in patients with short P–R intervals and normal QRS complexes; second, to clarify the relation of such cases to those of the Wolff-Parkinson-White syndrome; and third, to determine whether these patients have distinctive features in common which will facilitate their clinical recognition.

INCIDENCE OF PAROXYSMAL TACHYCARDIA IN SHORT AS COMPARED WITH NORMAL P-R GROUPS

Material and Methods

This study is based on 200 patients with a P–R interval of 0.12 second or less, referred to as the short P–R group, and an identically selected group with normal P–R durations serving as a control. Half of the 200 cases in the control series had A–V conduction times of 0.16 and the other half of 0.18 second. Our material was obtained from 13,500 consecutive electrocardiograms taken at the Peter Bent Brigham Hospital from 1947 through 1950. During

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard School of Medicine, Boston, Mass.

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this time the length of P–R (or P–Q) intervals has been ascertained and noted routinely on all tracings. Our cases were obtained from such lists and all P–R durations were remeasured in the accepted manner.[15] Case histories were not perused until after the measurement of the P–R duration; thus subjective factors were kept at a minimum during the phase of material selection. If, on remeasurement of the A–V conduction time, a patient had at least one electrocardiogram with a P–R duration of 0.16, 0.18, or 0.12 second or less, his record was studied.

The diagnosis of 760 patients showing the designated values for A–V conduction were examined. All patients with conditions that may either affect P–R duration or induce rapid heart action were eliminated. The purpose was to isolate a group in which no known factors appear to be involved that may modify the type of electrocardiogram and a tendency to tachycardia. The conditions which were thus excluded were:

1. Rate greater than 100 on all electrocardiograms with selected P–R interval.
2. No electrocardiogram available with patient off digitalis and quinidine.
3. Rapid heart action only while digitalized.
4. Rheumatic heart disease and acute rheumatic fever.
5. Thyrotoxicosis and patients on thyroid medication.
6. Coronary artery disease manifested by angina pectoris or myocardial infarction, old or recent.
7. Eisenmenger's complex and tetralogy of Fallot.
8. Bronchogenic carcinoma.
9. Nodal rhythm and wandering pacemaker.
10. Inadequate history.

Since tachycardia tends to shorten the P–R interval, patients with rates over 100 in all their tracings, even though they possessed the selected P-R's, were eliminated from this study. The failure to obtain an electrocardiogram while a patient was not taking digitalis or quinidine or the development of rapid heart action while taking digitalis constituted a basis for exclusion. This was done not only because digitalis and quinidine affect A–V conduction time but also because of the accumulating evidence that digitalis in overdosage may induce paroxysmal auricular tachycardia.[16, 17] Conditions such as rheumatic fever, valvular disease and thyrotoxicosis, known either to predispose to or induce auricular arrhythmias, were eliminated. Since nodal rhythm manifested by an upright P wave in lead aV_R or an inverted P in leads II and III frequently arises in a background of coronary artery disease, cases with these abnormalities were not included in the short P–R group.

Employing this process of selection, 200 patients with short P–R and 200 control patients with normal P–R intervals were chosen. Once a patient was included in the study, the medical history was carefully examined to determine the presence or absence of paroxysmal tachycardia. On the basis of these findings each case was further classified into one of three categories: (1) Those with definite paroxysmal rapid heart action, wherein electrocardiographic or medical substantiation of the recurrent tachycardia existed; (2) those with suggestive histories of bouts of rapid heart action but with inadequate medical corroboration—the mere presence of palpitation was not a sufficient criterion for inclusion in this group; and (3) those without rapid heart action.

Results

The incidence of paroxysmal rapid heart action in the short and normal P–R groups is summarized in table 1. Among the 200 cases with P–R intervals of 0.12 second or less there were 23 patients with proved paroxysmal tachycardia, while among the 200 patients with P–R intervals of 0.16 and 0.18 second there was only one such case. Histories suggestive but not diagnostic of rapid heart action were also twice as common in the short P–R as compared with the control series.

In table 1, cases in the short P–R group are also classified on the basis of the presence or absence of anomalous A-V conduction of the Wolff-Parkinson-White variety. Our definition of the Wolff-Parkinson-White syndrome included not only patients with typical "Eiffel Tower" QRS configuration, but also those with the slightest slurring of the ascending foot of the QRS irrespective of its duration and those with bundle branch block and P–R intervals of 0.12 second or less. There were four cases with bouts of rapid heart action among the 16 cases considered to have the Wolff-Parkinson-White syndrome as compared with 19 among the 184 with short P–R and normal QRS. Five of the 16 cases designated as having the Wolff-Parkinson-White syndrome had bundle branch block in conjunction with P–R durations of 0.12 second. Such cases may not be instances of anomalous A-V conduction but merely represent the superimposition of bundle branch block on a pre-existing condition of rapid A-V impulse transmission. In the former QRS prolongation is contingent upon P–R shortening, while in the latter the two are but coincidentally associated. In a

short P–R population selected as indicated, there are five times as many cases with paroxysmal rapid heart action with QRS complexes free of aberration as in a population with the Wolff-Parkinson-White configuration; this notwithstanding the higher relative incidence of tachycardia in the latter group.

The 200 short P–R and 200 control cases were compared to assess the presence of factors other than A-V conduction which may play a role in the genesis of the tachycardia. The only difference encountered in the two populations that may be of significance was a disparity of sex distribution and an unequal incidence of psychoneurosis and Addison's disease. There

TABLE 1. *Over-all Results: Incidence of Paroxysmal Rapid Heart Action in the 200 Cases with Short P–R Intervals and 200 Controls*

	Short P–R	Control
Cases with Normal QRS Complexes		
Rapid heart action	19	1
Suggestive	15	7
No rapid heart action	150	192
Cases with Abnormal QRS Complexes (Wolff-Parkinson-White)		
Rapid heart action	4	0
Suggestive	1	0
No rapid heart action	11	0
	200	200

were 55 per cent females in the short P–R compared with 45.5 per cent in the normal P–R group. Psychoneurosis was nearly twice as prevalent in the short P–R than in the control series, while Addison's disease had a fourfold higher incidence in the control group. From the comparison of these populations two other differences emerge which further characterize the short P–R group. First was the relative constancy, over the course of years, of the A-V conduction time in the short P–R cases, and second was their possession of a snapping apical first heart sound. In patients with more than one electrocardiogram P–R interval variations up to 0.02 second were encountered in 20 per cent of the short P–R against 65 per cent of the control group. The intensity of the first apical sound, when commented upon, was noted as accentuated in 87 per cent of the short P–R as compared with 21 per cent of the control series.

If among patients with accelerated A-V conduction time there is an increased occurrence of paroxysmal tachycardia, a converse relation should also be apparent, namely, an augmented incidence of short P–R intervals among similarly selected patients with recurrent bouts of rapid heart action. The investigation of the validity of such a relation requires a knowledge of the usual P–R distribution in our routine electrocardiographic population. In determining this distribution we followed the criteria given above and excluded condi-

TABLE 2. *The Distribution of Duration of A–V Conduction Time in 15 Patients with Proved Paroxysmal Tachycardia. The predicted incidence is based on a sampling of P–R distribution in 539 cases.*

PR Interval	Number of Cases	
	Observed Incidence	Predicted Incidence
0.12 sec. or less	6	1
0.13 sec.	5	1
0.14 sec. or over	4	13
	15	15

Wolff-Parkinson-White syndrome—0

tions which are known either to affect A-V conduction or to predispose to paroxysmal tachycardia. In 539 consecutive patients selected in this manner 6 per cent had P–R intervals of 0.12 second, 6 per cent of 0.13 and 88 per cent of 0.14 second or more. This distribution approximates that reported in the literature.[18]

We thereupon chose 50 consecutive cases of paroxysmal supraventricular tachycardia from the records of the Peter Bent Brigham Hospital. Again following the criteria presented above, we excluded 13 because of coronary artery disease manifested either by angina pectoris or previous myocardial infarctions. Twelve were eliminated because of continued digitalization or the absence of an electrocardiogram after cessation of the bout of rapid heart action. Ten other patients excluded had

either thyrotoxicosis, rheumatic heart disease or carcinoma of the lung. The results of the distribution of A-V conduction time in the remaining 15 with bouts of rapid heart action are shown in table 2. Though the sample is small, nevertheless the results are statistically significant. While the 6 per cent incidence of P–R intervals of 0.12 second duration would predict one of the 15 to have a short P–R, the actual finding was six. Similarly, instead of the anticipated one patient with a P–R of 0.13, there were five such cases. While 13 of the 15 should have had P–R intervals exceeding 0.14 only four were observed to fall in this range and it is of interest that three of these four were over 70 years of age. Since this series is small, it precludes definite judgment; it suggests, however, that shortened A-V conduction time bears intimate relation to the occurrence of paroxysmal rapid heart action.

TABLE 3. *Cases with Paroxysmal Rapid Heart Action. Comparison of the Wolff-Parkinson-White Syndrome with Short P-R–Normal QRS Cases.*

	Short PR Normal QRS (34 cases)	Wolff-Parkinson-White (55 cases)*
Age at onset of tachycardia		
Average	33.5	22.5
Range	10–61	1–54
Sex, Female	70.9%	32%
Mitral first sound accentuated	87% *of 23 cases*	16% *of 14 cases*
Premature beats	34% *of 34 cases*	13.5% *of 37 cases*
ECG		
Slurring of R on upstroke	absent	present
Onset of R (range)	0.02–0.04 sec.	0.03–0.011 sec.
Onset of R (average)	0.026 sec.	0.074 sec.
QRS duration (range)	0.04–0.08 sec.	0.09–0.16 sec.
QRS duration (average)	0.07 sec.	0.13 sec.
Usual PR	0.12 sec.	0.09 sec.
Constancy of PR	6% varied more than 0.01	43.7% reverted to normal conduction
Usual PJ interval	0.19 sec.	0.22 sec.

* Selected from 29 cases in present series and 60 cases in the literature. See text.

Comparison of Patients with Short P–R, Normal QRS and Paroxysmal Tachycardia with Those with the Wolff-Parkinson-White Syndrome

Material and Methods

Thirty-four patients with paroxysmal rapid heart action, short P–R duration and normal QRS complexes were compared with 55 with Wolff-Parkinson-White configuration who also exhibited recurrent tachycardia. Nineteen of the 34 patients were obtained from our present study while 15 were found in the private files of one of us (S. A. L.). The two groups with short P–R and normal QRS were comparable in nearly every respect. To permit comparison the Wolff-Parkinson-White patients were chosen in a manner similar to those who had a normal QRS complex. The 55 with Wolff-Parkinson-White were selected from 89 cases with paroxysmal tachycardia along the criteria mentioned above. Twenty-nine of the 89 came from our files while 60 were chosen from cases reported in the literature.[1, 4, 10, 15–28] In order not to bias sex distribution, reports emanating from veterans hospitals or the armed forces were excluded as a source of Wolff-Parkinson-White material.

Results

The significant differences between patients having paroxysmal tachycardia with normal QRS complexes and those with Wolff-Parkinson-White configuration are shown in table 3. The patients with normal QRS complexes, unlike those with anomalous A-V conduction, had the onset of tachycardia a decade later in life. The most striking clinical difference in the two groups was the sex distribution. While two-thirds of the patients with the Wolff-Parkinson-White syndrome were males, two-thirds of cases with normal QRS patterns were females. The female preponderance was of the same magnitude both in the 15 private and in the 19 hospitalized patients. Among those who had descriptions in their case records of the intensity of the first apical heart sound, it was characterized as accentuated in nearly 90 per cent of those with the normal QRS complexes in contrast to 16 per cent of those with the Wolff-Parkinson-White syndrome. Premature beats, both auricular and ventricular, were

also more frequent in the group having a normal QRS.

The electrocardiographic pattern provided the main distinguishing features between the short P–R-normal QRS entity and the Wolff-Parkinson-White syndrome. In the normal QRS group the onset of the peak of the R wave was early and devoid of slurring, normalization was absent, the duration of P–R time was greater while that of the QRS and P–J interval was less than among cases with anomalous A-V conduction.

The configuration of the QRS complex was the critical point of distinction between the two groups. The presence in any case of a delta,[29] that is, a slurring of the initial portion of the QRS, irrespective of the length of this complex, sufficed for its inclusion into the Wolff-Parkinson-White category. We found that the measurement of the duration from the onset of the R wave to its peak served as an index of the extent of the slurring. When this measurement was 0.04 second or less no deformity of the ascending limb of the QRS was visible. The average duration from the beginning to the peak of the R wave was 0.074 while the total QRS measured 0.13 second in the 55 patients with the Wolff-Parkinson-White syndrome. In contrast, in the 34 with normal QRS complexes the respective values were 0.026 and 0.07 second.

In selecting the short P–R patients from whom the normal QRS group with tachycardia was obtained, we arbitrarily chose 0.12 second as the upper limit for A-V conduction. It is of interest that, within this limitation, the cases with a normal QRS and tachycardia had a very narrow range of P–R distribution. Only one of the 34 patients had an A-V conduction time of 0.10 second and in no instance was it shorter. The cases with the Wolff-Parkinson-White syndrome, however, rarely had P–R intervals which equaled 0.12 second; usually their P–R intervals were 0.10 second or less.

The constancy of P–R interval on repeated electrocardiograms in the same individual is a feature of the patients with normal QRS complexes and bouts of rapid heart action. Only six of the 34 patients under study showed a spontaneous variation in the P–R interval greater than 0.01 second on repeated electrocardiograms. In some instances, the time interval between tracings was as long as 10 years. Such stability was absent in patients with the Wolff-Parkinson-White syndrome, 43 per cent of whom showed "normalization." This refers to the reciprocal relation between the P–R and QRS durations manifested by the simultaneous lengthening of the former interval when the latter is shortened. In patients of the normal QRS group the P–R varied independently of the QRS which usually remained fixed in duration.

The P–J interval is another feature reflecting the difference between the two categories of short P–R. The P–J interval is measured from the inception of the P wave to the junction between either the R or S wave and the base line. The P–J interval in patients with Wolff-Parkinson-White syndrome is of normal duration and relatively constant irrespective of whether the underlying mechanism is one of either normal or anomalous conduction. In the normal QRS group the P–J was short, with an average value of 0.19 second. In the 34 cases it never exceeded 0.20 second, while patients showing Wolff-Parkinson-White syndrome usually had P–J intervals above this figure. In any one case with a normal QRS the P–J seldom varies; this is due to the relative constancy of the P–R interval.

The electrocardiogram of the patient with short P–R, normal QRS and paroxysmal rapid heart action is easily distinguished from that of the patient whose tracing shows the features characteristic of the Wolff-Parkinson-White syndrome. An occasional case defies categorization. Figure 1 represents the spectrum of QRS variation encountered among patients with short P–R intervals and paroxysms of rapid heart action. The tracing at *A* is a typical example of the syndrome under discussion, distinguished by a normal QRS complex devoid of slurring and a short P–R interval. The tracing at *B* demonstrates the characteristic "Eiffel Tower" pattern of the Wolff-Parkinson-White syndrome. The distinct delta in the tracing at *C* defines it as a case of anomalous

A-V conduction, notwithstanding the fact that the duration of the P–R and QRS are 0.11 and 0.09 second respectively. The tracing at *D* represents a case of short P–R (0.12 second) in combination with right bundle branch block. While this type of configuration has been regarded as a variant of the anomalous A-V conduction pattern, it may be an example of the entity being described wherein bundle branch block has supervened. This is the type of pattern which, in the absence of evidence of a reciprocality between P–R and QRS duration, eludes classification. The large majority of patients with short P–R and tachycardia, however, can easily be grouped into either the Wolff-Parkinson-White or the normal QRS category.

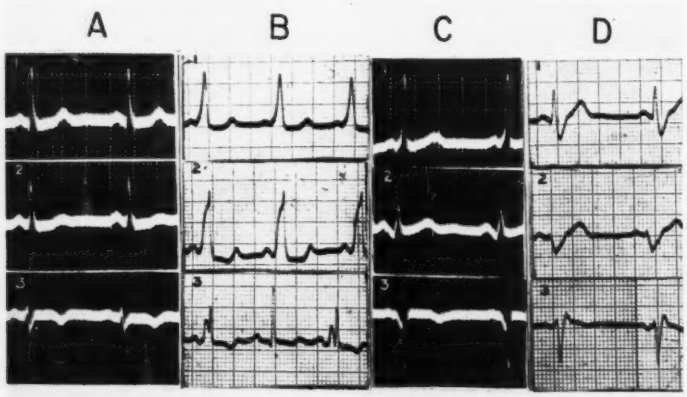

FIG. 1. Four patients with tachycardia and short P–R but with differing QRS configurations. *A*. Normal QRS complex. The patient was a 39 year old woman who experienced repeated paroxysms of auricular tachycardia. Electrocardiograms between bouts of rapid heart action taken 10 years apart were nearly identical. *B*. Typical example of the Wolff-Parkinson-White syndrome. In lead III spontaneous normalization for one beat is present. *C*. QRS of normal duration, but with a definite delta. *D*. Right bundle branch block.

CLINICAL FEATURES OF PATIENTS WITH SHORT P–R, NORMAL QRS AND PAROXYSMAL TACHYCARDIA

In a group of subjects with short P–R intervals and normal QRS complexes, selected as indicated, 10.4 per cent had recurrent rapid heart action. The majority of the patients with tachycardia were females in middle life who on examination were found to have a snapping first apical heart sound. While the average age of onset of tachycardia was 33.5 years, in a significant number the inception was late in life. In 14 of the 34 the first manifestation of tachycardia occurred after the age of 40. In eight of these rapid heart action was first noted after the age of 60. While palpitation was the chief and at times the sole complaint in 20 or 58 per cent of the patients, in the nine who had the onset of tachycardia after the age of 40 no preceding history of palpitation was obtained. In this older group bouts of rapid heart were precipitated by noncardiac ailments, trauma or anesthesia; prior to the onset of tachycardia, however, they already exhibited short P–R intervals in their electrocardiograms. In the majority of the patients under 40, no precipitating causes or predisposing factors for the tachycardia were evident. In one patient a severe emotional shock launched the first bout of rapid heart action, but subsequent episodes came without any preceding emotional upheavals. In another patient tachycardia occurred only during menstruation and in three rapid heart action appeared to be triggered by asthmatic attacks. Familial factors existed in two patients: one had a sibling who also showed

recurrent rapid heart action; the other, a middle-aged woman, had a son with tachycardia and a short P–R interval.

The tachycardia, once it appeared, recurred sporadically with intervals between attacks varying from a few hours to many years. The longest history of recurrent rapid heart action was 60 years and was noted in two patients. The most frequent arrhythmia was paroxysmal auricular tachycardia. Twelve patients exhibited this type of rapid heart action, six experienced bouts of auricular fibrillation, four had flutter and one had nodal tachycardia, while another had paroxysmal auricular tachycardia with block. Three patients had more than one type of rapid heart action. The remaining patients had supraventricular tachycardia of unspecified type. The majority of patients tolerated the rapid heart action well. This was due, in all likelihood, to the absence of underlying organic heart disease. Two patients, however, died suddenly. Both of these were subject to paroxysms of auricular fibrillation. No postmortem examinations were available to ascertain whether death was due to pulmonary embolism.

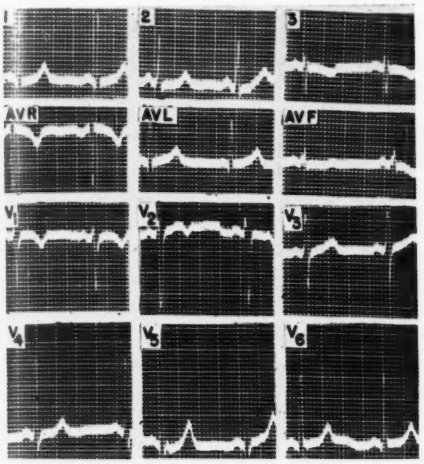

FIG. 2. Electrocardiograms of a 50 year old woman (Peter Bent Brigham Hospital #172032) who complained of palpitation for 10 years, demonstrated to be due to paroxysmal auricular tachycardia. Except for a P-R interval of 0.12 second her electrocardiogram is within normal limits.

The customary methods of prevention and control of attacks were employed in these cases. Prevention proved more difficult than control. Maintenance of digitalis or constant quinidine administration decreased the incidence of paroxysms in many instances. The greatest harm in the care of these patients is the frequent attribution of coronary artery or arteriosclerotic heart disease as the cause of the recurrent tachycardia. The realization that the tachycardia is self-limited in duration, of benign genesis and usually without deleterious sequelae helps the physician provide the patient with assurance and a proper perspective of the disorder.

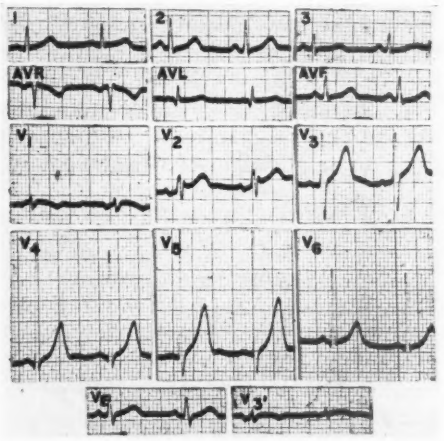

FIG. 3. Electrocardiogram of a 13 year old girl (S.A.L. #A8660) who had paroxysmal auricular tachycardia for three years. The P-R had a duration of 0.12 and the QRS of 0.06 second.

The combination of clinical features in patients with short P–R, normal QRS and paroxysms of tachycardia is distinctive and possible of easy recognition. (See figs. 2, 3.) The presence of palpitation of sudden onset and offset, which is controlled by deep breathing, gagging, or carotid sinus pressure in a middle-aged woman, is suggestive of this entity. The presence of a snapping first apical heart sound without any stigmas of heart disease should further enhance suspicion, while the persistence of a short P–R interval in conjunction with a QRS complex devoid

of any slurring on its upstroke is corroborative.

Discussion

The difference in incidence of rapid heart action in the series of patients with short P–R intervals and in the control series with normal P–R intervals, even after the exclusion of all cases with the Wolff-Parkinson-White syndrome from the former, is statistically significant. The question still arises whether the two populations compared are not artefacts of selection. A concrete answer to the problem is contained in the excluded population. Three hundred sixty patients were excluded from this study because they had conditions which either modified the P–R duration or predisposed to rapid heart action. About half of these patients had short P–R and half had normal P–R intervals. If defective methods of selection had been employed, by means of which most of those with paroxysmal rapid heart action and short P–R were included while the majority of those with normal P–R and rapid heart action were excluded from this study, then the incidence of recurrent tachycardia in the excluded control population would have exceeded significantly that in the excluded group with short P–R intervals. This excess would have roughly approximated the preponderance of patients with tachycardia in the short P–R as compared with the control group under study. This was not the case. The frequency of paroxysmal rapid heart action was similar in the two excluded groups irrespective of the length of the P–R interval. The elimination of known causes of rapid heart action, therefore, accents the relation between shortened A-V impulse transmission and recurrent tachycardia. We dwell on this point because to date, except for the special phenomenon of anomalous A-V conduction, no general recognition of such a relation exists. The reason for this has been failure to exclude all conditions which may precipitate tachycardia when the role of short P–R is under investigation. In our study, among 380 cases with short P–R intervals and among an equal number of controls there were 74 patients with paroxysmal rapid heart action, 46 in the former and 28 in the latter category. In the selected group under study, however, among the 200 patients with short P–R intervals, there were 23 with tachycardia compared with one among the 200 patients with normal P–R durations. Obviously when exclusion of other causes of tachycardia is not carried out, the role of the P–R interval is inundated among a host of other factors.

Our data do not establish whether the high incidence of tachycardia in patients with P–R durations of 0.12 second or less is a special feature for this range of A-V time or is merely a reflection of an augmented frequency of tachycardia as the P–R shortens. We arbitrarily chose 0.12 second as the upper limit for our short P–R category. For adults this is regarded by Scherf[30] as the lowest normal value. It may be that a similar incidence of tachycardia exists for patients with P–R intervals of 0.13 second. The evidence available at present suggests that with shortening of the P–R interval there is an increasing incidence of rapid heart action. Among 200 patients with P–R intervals of 0.16 and 0.18 second the frequency of bouts of tachycardia is 0.5 per cent. Among 184 patients with P–R intervals ranging from 0.10 to 0.12 second it is 10 per cent, while the reported incidence of recurrent tachycardia in large series of subjects with the Wolff-Parkinson-White syndrome, generally having P-R intervals of 0.08 to 0.11 second, is given as 70 per cent. It may be that the tachycardias occurring in patients with Wolff-Parkinson-White syndrome are not special results of anatomic anomalous A-V pathways, but merely the accentuated manifestation of the operation of the same physiologic factors as in those instances where A-V conduction time is shortened.

Until this present study 11 patients have been described in the literature with short P–R intervals, normal QRS complexes and recurrent tachycardia. In a paper on paroxysmal tachycardia by Wedd,[8] which appeared in 1921, a typical case with this syndrome is presented. This article is of historic interest since it reports the second case with the distinctive features which have now come to be recognized as characteristic of the Wolff-Parkinson-White syndrome, and, to our knowl

evidence, the first case of the entity which we are describing.

In 1938 Clerc and co-workers[9] described three such patients with short P–R, normal QRS and rapid heart action. These three were obtained from 21 cases with short P–R intervals who were free of stigmas of relevant heart disease. This is approximately the same incidence of tachycardia which we found in our much larger series of patients with short P–R intervals. Over half of the 21 patients of Clerc and associates suffered from palpitation. Seven who were available for long-term follow-up studies showed no alteration of their A-V conduction time. These authors also noted that in two instances vagal stimulation and exercise and in one case digitalis did not alter the P–R duration or the QRS configuration. The seven other patients described in the literature[10–14] have been considered by the authors as variants of the Wolff-Parkinson-White syndrome. They have been categorized as examples of either the normal or the anomalous conducting phase of Wolff-Parkinson-White syndrome. The following facts, however, are against their being manifestations of the "normalized" phase: (1) the failure to observe the aberrant stage of conduction in those patients followed for many years; (2) the lack of reciprocal changes in the QRS duration in those few patients exhibiting P–R interval prolongations; (3) the higher incidence of patients with short P–R, normal QRS and tachycardia compared with those with the Wolff-Parkinson-White syndrome. One would anticipate a random distribution of P–R durations during the "normalized" phase of the Wolff-Parkinson-White syndrome, and therefore only about 6 per cent would have P–R intervals of 0.12 second.

An alternate explanation is that these are manifestations of the Wolff-Parkinson-White syndrome during the aberrant phase of A-V conduction. Burch[31] suggests that the accessory bundle in these patients terminates in the interventricular septum near its base or in the bundle of His. On the basis of earlier views[2, 3] of the pathogenesis of anomalous conduction, it was possible by "positioning" the single bundle of Kent to explain nearly all short P–R tracings as those of the Wolff-Parkinson-White syndrome. Current views, however, cast doubt on the existence of a single, discrete, short-circuiting path resulting in pre-excitation with ensuing asynchrony in both action potential production and mechanical systole of the two ventricles. Glomset and Glomset[32] have shown that most mammalian hearts have multiple muscular bridges between auricles and ventricles. Rosenbaum and his associates[28] by means of chest and esophageal leads were the first to suggest that pre-excitation occurs simultaneously in both ventricles. Grishman and co-workers[33] with the aid of intracardiac and esophageal electrocardiography confirmed and further extended these findings. Their observations indicate that the abnormally propagated impulse reaches simultaneously the anterior surface of the right ventricle and the posterior epicardial and endocardial surfaces of the left ventricle. Conduction through the normal pathways apparently does not occur. Hemodynamic studies[34] in patients with Wolff-Parkinson-White syndrome, by means of right heart catheterization, show a delay in the interval between the Q wave of the electrocardiogram and both the inception of right ventricular systole and the onset of the pressure rise in the brachial artery. Electrokymographic studies[35, 36] further confirm these findings by the demonstration of delayed and synchronous pulmonary and aortic systolic impulses in patients with the Wolff-Parkinson-White syndrome. The paradoxic clinical finding of a normal or muffled first apical heart sound in the Wolff-Parkinson-White syndrome, notwithstanding the ultra short P–R, is in accord with the above observations. Normally the P–R duration is closely correlated to the intensity of the first heart sound.[37–39] The shorter the interval, the more intense is the first heart sound. In the Wolff-Parkinson-White syndrome, notwithstanding the short P–R, there is a delay in ventricular systole caused by the aberrant slow ventricular depolarization. The delayed contraction permits the A-V valves to float up, with a maintenance of the normal intensity of the first heart sound. Current theory holds, therefore, that the Wolff-Parkinson White syndrome is due to a filtering down of

auricular impulses along many tracts with pre-excitation of both ventricles. The impulses are propagated aberrantly through the ventricles and result in simultaneous but delayed ejection of blood into the pulmonic and aortic circuits.

Wolff and White[4] have regarded these cases of short P–R and normal QRS as instances of anomalous conduction wherein the speed of impulse transmission in the accessory tracts approximates that of the normal pathway. The fulfillment of such a condition would obviate the slurring of the ascending limb of the QRS as well as the reciprocal changes in P–R and QRS duration observed in patients with the Wolff-Parkinson-White syndromes. To sustain such a supposition three further assumptions are necessary: first, that the abnormal pathways have relatively slow rates of conduction; second, that these rates of conduction are nearly identical in all the different muscular connecting bridges; and third, that the normal pathways have relatively rapid conduction times approximating those of the accessory tracts. However, the independence of relation between A-V conduction and QRS duration in some of these patients indicates the operation of a mechanism other than anomalous conduction. In a patient currently under study (not included in the series), vagal stimulation by carotid pressure, parasympathomimetic drugs, atropine, exercise and quinidine caused no significant alteration in the P–R time. With a marked overdosage of digitalis, A-V time was lengthened to 0.15 second; however, the QRS remained fixed in duration. Immediately after a bout of paroxysmal auricular tachycardia with a rate of 190, the P–R interval was observed to be 0.14 second; again the QRS remained unaltered.

A further difficulty in the categorization of these patients as having Wolff-Parkinson-White syndrome is the short duration of their QRS complex. If these cases had usual P–R intervals of 0.13 or 0.14 second and an abnormal pathway conducting at 0.12 second, one would expect the QRS in a large series of these patients to be slightly longer than normal. During aberrant impulse propagation the increment of P–R shortening would be added to the QRS length. The 34 patients with short P–R, normal QRS and tachycardia had an average duration of the QRS complex of 0.071 second. For the 165 patients with short P–R but without tachycardia it was 0.073, while for the 200 patients with normal P–R intervals it was 0.079 second. If the condition of short P–R and normal QRS is due to the presence of congenital aberrant auriculoventricular communication, tachycardia might be expected to appear early in life as in the Wolff-Parkinson-White syndrome. This, however, was not the case. In nearly half it occurred after the fortieth year and in one-fourth of the patients after the sixtieth year of life. The incidence of males with Wolff-Parkinson-White is 70 per cent, while the incidence of males with short P–R, normal QRS and tachycardia is 30 per cent. This striking sex discrepancy further points to a fundamental difference between the two conditions.

Our conclusion, therefore, is that the combination of short P–R, normal QRS and bouts of rapid heart action constitutes a distinct entity and is not an expression of anomalous conduction. The increased incidence of tachycardia in both conditions may, however, be a reflection of those changes brought about by, or associated with, the shortened A-V conduction time.

Some authors have considered electrocardiograms with positive P waves in the limb leads and P–R intervals of 0.12 second or less as a type of coronary sinus nodal rhythm.[40–42] Scherf and others[43, 44] regard this as regular sinus rhythm and require deeply inverted P waves in leads II and III for the definition of coronary sinus rhythm. However, even if the former criteria for coronary sinus rhythm are entertained, patients with this form of nodal rhythm differ in many respects from the patients with short P–R intervals and tachycardia. This type of nodal rhythm usually is associated with a P–R of less than 0.10 second, the heart rate is under 50, the nodal rhythm almost invariably is transient and when permanent reflects serious myocardial injury; furthermore, it is not accompanied by paroxysms of rapid heart action.

A study of the conditions that predispose

to shortened A-V conduction time sheds some light on the possible background factors of the syndrome of short P–R, normal QRS and recurrent rapid heart action. During infancy the P–R interval is short and assumes an adult pattern at about the time of puberty.[45, 46] Söderström[13] in 30 patients with short P–R intervals observed an increased occurrence of hyperthyroidism and acute myocardial infarction. In the latter condition the short P–R interval was observed during the early stages of the infarction and subsequently it increased in length. In 84 patients with acute coronary thrombosis whom we recently studied[47] we noted that nearly one-fourth of the patients had transient shortening of A-V time to levels of 0.12 to 0.13 second. This occurred during the first week of the illness. Scherf[48] found hypertension in 29 out of 49 patients with P–R intervals of 0.11 second or less. Two of the patients with short P–R had hyperthyroidism. He concludes that a short P–R is associated with a "marked hypermotility and hypercontractibility of the heart."

Thorn, Dorance and Day[49] have shown that 21 per cent of patients with Addison's disease who show some abnormality in the electrocardiogram have first degree heart block. This has been confirmed by Sommerville and associates.[50] In a preliminary study we find that nearly all addisonian patients have P–R durations of 0.16 second and over; while patients with Cushing's syndrome have P–R's of 0.14 or less. Furthermore, in a number of patients now under observation, the administration of cortisone or adrenocorticotropic hormone (ACTH) has caused a shortening of the P–R interval. In the treatment of acute rheumatic fever with cortisone or ACTH one of the earliest changes in the electrocardiogram is a decrease in the A-V conduction time. The conditions which are reported to be associated with a short P–R are known to exert potent stress on the adaptive processes of the body. In some patients anxiety neurosis is accompanied by evidence of increased adrenocortical activity manifested by a chronically depressed fasting eosinophile count.[51] This is of interest in the light of Ruskin's observation[52] that there is a frequent co-existence of mental disease and a short P–R interval without P-wave abnormality. In a recent report Rovrik and Aarstrand[53] have concluded that shortening of the P–R interval is one of the characteristics of the electrocardiogram in the neurotic female. This is in agreement with our observation. In the short P–R series neurosis was twice as common as in the control population. Since the incidence of neurosis among the males was the same in the two groups, the increase is accounted for by a marked preponderance of females with neurosis and short P–R.

Another mechanism invoked to explain the co-existence of short P–R and neurosis is increased sympathetic tone which is a resultant of the state of chronic tension. Such an explanation may be utilized also to account for the association of short P–R and paroxysmal rapid heart action. It is fairly well established that sympathetic stimulation is associated with a shortening, while parasympathetic stimulation is associated with a lengthening, of the P–R duration.[54, 55] Standing, which increases sympathetic tone, may shorten the P–R duration in some individuals[56, 57] and may precipitate paroxysmal tachycardia which is relieved by lying down.[58] Cervical and upper dorsal sympathectomy has been utilized to do away with troublesome recurrent superventricular tachycardias.[59] Forty years ago Rothberger and Winterberg[60] induced auricular fibrillation by the simultaneous stimulation of the sympathetics and the vagus. The intravenous administration of small amounts of acetylcholine and adrenaline will likewise produce auricular fibrillation in a high percentage of cases.[61] Many of the conditions reported to shorten the P-R duration such as hypertension, thyrotoxicosis and anoxia increase sympathetic tone as a part of the homeostatic response of the individual. Classic physiologic studies have furnished evidence that there is a sympathetic center in the hypothalamus. Bronk and his colleagues[62] have induced impulses in efferent sympathetic nerves during hypothalamic stimulation and conversely showed rhythmic variations in potential in the hypothalamic nuclei by the stimulation of efferent nerves possessing sympathetic fibers. Deduc-

tions from animal experiments have led to the supposition that emotional instability is associated with hypothalamic overfunction due to a release from higher cortical centers.[62] The presence of "autonomic imbalance" has therefore been utilized to account for the short P–R interval in mental disease.

Hume and Wittenstein[64] have presented evidence that the hypothalamic centers have a regulatory influence over pituitary adrenocorticotropic activity. Thus the intermediary pathways of hypothalamic activity, be they endocrine or sympathetic nervous system in mechanism, tend to shorten the P–R interval. Furthermore, there is a great deal of data, both of a clinical and experimental nature, to suggest that the hypothalamus may initiate some cardiac arrhythmias.[65–68] The hypothalamic lead of the electroencephalogram is abnormal in patients with paroxysmal rapid heart action when there is no heart disease; however, when there is organic disease of the heart and tachycardia the electroencephalogram is normal.[69] The evidence presented invites the speculation that in certain individuals chronic stress with resultant hypothalamic discharge activates the adrenal cortex and the sympathetic nervous system. These in turn sustain shortened A-V conduction times and with periodic augmentation of stress these mechanisms trigger outbursts of tachycardia. While such a hypothesis is highly presumptive, it opens possibly fruitful avenues for the investigation of the genesis of the syndrome of short P–R, normal QRS and paroxysmal rapid heart action.

Summary and Conclusion

1. In a selected group of 200 patients with short P–R intervals there were 23 patients or 11 per cent with paroxysmal tachycardia compared with 1 or 0.5 per cent in a similarly selected control group of 200 with normal P–R durations.

2. Among the 200 patients with a short P–R interval, 184 had normal QRS complexes and 16 had Wolff-Parkinson-White configurations. The incidence of paroxysmal tachycardia was 10.4 per cent in the former group and 25 per cent in the latter.

3. Of the 23 patients with recurrent bouts of rapid heart action and short P–R, 82 per cent had normal QRS complexes while 18 per cent possessed the features of the Wolff-Parkinson-White syndrome.

4. The patients with a short P–R interval, normal QRS complex and bouts of rapid heart action exhibit a different electrocardiographic pattern from patients with the Wolff-Parkinson-White syndrome. Their QRS, unlike that of Wolff-Parkinson-White, is devoid of slurring and does not exceed 0.08 second in duration; they do not show normalization and have shorter P–J and P–R intervals which are strikingly constant over the course of years.

5. Short P–R, normal QRS and recurrent tachycardia is a distinct and easily recognizable clinical entity. It occurs predominantly in the female sex, the tachycardia in half the patients begins after the fourth decade of life, a third of the patients have premature beats and the majority show an accentuation of the first apical heart sound. In these respects, this entity further differs from Wolff-Parkinson-White syndrome.

6. Evidence is presented that the mechanism underlying short P–R, normal QRS and tachycardia is not one of anomalous A-V conduction and pre-excitation as is believed to be the case in the Wolff-Parkinson-White syndrome.

7. The implication from this study and from pertinent medical literature would lead one to explore the possible relationship between the endocrine system (particularly the adrenals) and autonomic nervous system on the one hand and the shortening of the P–R interval and paroxysms of tachycardia on the other.

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Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction

By Henry I. Russek, M.D., Burton L. Zohman, M.D., Alexander A. Doerner, M.D., Allen S. Russek, M.D., and LaVere G. White, M.D.

Many physicians find it difficult to decide whether or not a patient sustaining a mild episode of acute myocardial infarction should be treated with anticoagulant drugs. The Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Occlusion with Myocardial Infarction (American Heart Association) has recommended the employment of such therapy in patients with this disease, unless contraindications to anticoagulant therapy exist. Data are presented to show that in "good risk" patients treated conservatively without anticoagulants, the mortality rate and incidence of thromboembolism are strikingly low. Consequently, even the maximum benefit theoretically obtainable from the employment of dicumarol in these cases is not sufficient to justify the hazard entailed in its use. It is therefore recommended that anticoagulants be employed only in the more serious attacks of the disease.

ANTICOAGULANT therapy is now widely employed in the management of acute myocardial infarction, and, since it is a costly and burdensome form of treatment, the indications for its use should be clearly defined. Comparisons of unselected control and treated groups do appear to indicate that anticoagulants significantly reduce the over-all mortality rate and incidence of thromboembolism in this disease.[1, 2] From such crude statistics, however, it is by no means certain that these agents should be routinely prescribed in the treatment of all cases of acute myocardial infarction. The possibility must be recognized that the anticoagulant, like any other drug, may be indicated only under certain well-defined circumstances.

In a previous publication, the writers[3] pointed out that the results of conservative therapy in "uncomplicated" cases of acute myocardial infarction are unlikely to be improved (and may actually be made worse) by employment of bishydroxycoumarin (dicumarol). This conclusion was based upon an analysis of 424 cases of acute myocardial infarction which were treated by conservative methods at the U. S. Public Health Service Hospital in Staten Island and the Maimonides Hospital in Brooklyn, New York. By employing certain known prognostic criteria, it was found that 204 of these patients presented no unfavorable signs for recovery during the first 24 hours of hospitalization. The mortality rate for this "good risk" group was only 2.45 per cent. Moreover, when the fatalities which obviously could not have been avoided with bishydroxycoumarin were eliminated, the theoretically preventable mortality rate for this group was only 0.98 per cent. The incidence of thromboembolism was also less than 1 per cent. Inasmuch as the administration of bishydroxycoumarin, in itself, presents a small but definite risk to life, our findings appeared to challenge the current practice of prescribing this drug in all cases. The limited theoretic benefit from bishydroxycoumarin in the milder episodes of infarction did not seem to compensate adequately for the potential hazards of the induced hemorrhagic state.

In order to determine whether the low mortality rate which was observed among the "good risk" patients in our series might have

From the Cardiovascular Research Unit, Department of Medicine, United States Public Health Service Hospital, Staten Island, N. Y.

A joint project with the National Heart Institute, United States Public Health Service, Washington, D. C., in conjunction with the Medical Services of Kings County and Maimonides Hospitals, Brooklyn.

been purely the result of chance sampling, it was decided to investigate a new series of cases from an entirely different source. As in our previous study we established the following criteria as indicative of a guarded prognosis: (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter; ventricular tachycardia or intraventricular block, (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities in the lower extremities, thrombophlebitis (past or present) or other states predisposing to thrombosis. Patients who showed none of these symptoms during the first day of hospitalization were classified as "good risks" to distinguish them from the "poor risk" group comprising those who manifested one or more of these unfavorable prognostic signs.

Composition of Sample

All of the patients in the present series were treated at the Kings County Hospital (State University, College Division). Selection was made of consecutive admissions for acute myocardial infarction from hospital records covering a five year period. Of the 623 patients studied, 473 were male and 150 were female. A history of previous hypertension was obtained in 28 per cent of the men and in 47 per cent of the women. The ages ranged from 30 to 88 years with a mean age of 58.1. Forty-seven per cent of the patients were 60 years of age or older, compared with only 32 per cent of the patients in the former series. A considerably higher proportion of the subjects in the present group were admitted to the hospital within 24 hours of the onset of their attack than in the former analysis. In the classification of patients into "good risk" and "poor risk" groups only the facts in the history and physical examination which were available on the first day of admission to the hospital were considered. After such classification was complete, a study was made of the clinical course and subsequent outcome in each case. Inasmuch as the selection of "good risk" cases was independent of the data recorded in the histories after the first day of admission to the hospital and was made without knowledge of the final result in each instance, the element of bias is believed to have been excluded. Moreover, the fact that the clinical data were obtained and recorded years before by physicians not taking part in the present study seemed to obviate the possibility of prejudice and to add to the validity of this method of analysis. In every instance the clinical diagnosis of acute myocardial infarction was confirmed by one or more electrocardiograms. All of the patients were treated by conservative methods without the use of anticoagulants.

Results

Of the 623 patients, 247 died during the period of hospitalization, giving an over-all mortality rate of 39.6 per cent (table 1). This crude death rate, therefore, is considerably greater than that in the former study in which it was computed at 24.3 per cent. Clinical thromboembolic phenomena occurred in 44 patients or 7.1 per cent of the present series as compared with 4.5 per cent of the group previously analyzed. Of the 623 patients in the present series there were 285 who qualified as "good risk" according to our criteria. The mortality rate for this selected group was 3.5 per cent (table 1), an incidence approximating that observed for the comparable group in our earlier study (2.45 per cent).

When the causes of death were analyzed among the "good risk" cases in order to determine the number of fatalities which theoretically might have been prevented by bishydroxycoumarin, the following data were obtained: five of the total of 10 deaths took place within the first 48 hours of admission to the hospital before dicumarol could have exerted significant effect; of the remaining five deaths, two resulted from causes independent of the cardiovascular system (one from perforation of a peptic ulcer, the other from septicemia and bronchopneumonia), one was caused by recurrent myocardial infarction and two by undetermined causes. If it is assumed that the latter three patients might have survived as a result of bishydroxycou-

marin therapy (an assumption lacking confirmatory evidence), the theoretically preventable mortality for the 285 "good risk" patients in this series would be 1.1 per cent. A strikingly similar figure for theoretically avoidable deaths was noted in our previous study (0.98 per cent). Thromboembolism occurred in only 2 of the 285 "good risk" cases for an incidence of 0.7 per cent. The latter, therefore, confirms the infrequency of the complication in this class of patient as previously reported by the writers.

Eighty per cent of the "good risk" cases in the present analysis were admitted to the hospital on the day of their attack. This unusually high incidence of immediate admissions indicates that the low mortality rate reported for "good risk" patients did not result from distortion produced by their delayed entrance to the hospital. This is confirmed by the finding that the death rate for the 228 "good risk" patients admitted on the day of their attack was identical with that for the total group of "good risk" patients (3.5 per cent).

TABLE 1.—*Mortality Rate and Incidence of Thromboembolic Complications (Kings County Hospital Series)*

	No. Cases	Mortality		Embolization	
		No.	Percentage	No.	Percentage
Total	623	247	39.6	44	7.1
"Good Risk"	285	10	3.5	2	.7
"Poor Risk"	338	237	70.1	42	12.4

In striking contrast with these survival statistics were those obtained for the 338 "poor risk" cases which manifested unfavorable prognostic signs (table 1). Thus the mortality rate for the latter group was 70.1 per cent and the incidence of thromboembolic complications was 12.4 per cent. Death was, therefore, 20 times more frequent and thromboembolism 18 times more frequent in the "poor risk" than in the "good risk" group.

Inasmuch as the findings of the present study closely approximate those obtained in our previous analysis with respect to survival statistics for "good risk" patients it appears reasonable to assume that our data offer a true representation of mortality rate in such selected cases. The death rate and incidence of thromboembolic complications in the combined series, totaling 1047 cases, is shown in table 2. It can be seen that the mortality rate for 489 "good risk" cases, classified according to our criteria, was 3.1 per cent while the incidence of thromboembolic complications for the same group was 0.8 per cent. Of great significance is the fact that the preventable mortality for these selected cases, under bishydroxycoumarin therapy, could not have exceeded 1.0 per cent.

TABLE 2.—*Mortality Rate and Incidence of Thromboembolic Complications (Combined Series from Three Hospitals)*

	No. Cases	Mortality		Embolization	
		No.	Percentage	No.	Percentage
Total	1047	350	33.4	63	6.0
"Good Risk"	489	15	3.1	4	.8
"Poor Risk"	558	335	60.0	59	10.6

DISCUSSION

In spite of the volume of literature concerned with survival statistics in acute myocardial infarction, little or no information is available regarding the outlook for the patient sustaining an "uncomplicated" first attack. It has been claimed that a fatal outcome occurs in no more than 10 per cent of patients suffering their initial episode.[4] Master, Jaffe and Dack[5] reported a mortality rate of only 8 per cent in their series of cases with first infarctions. These figures, however, represent crude mortality statistics in unselected patients with attacks of varying severity. In our series of 489 "good risk" cases, all of whom sustained a first attack without serious initial symptoms, the mortality rate was only 3.1 per cent and the incidence of thromboembolism was only 0.8 per cent.

In order to determine whether bishydroxycoumarin should be administered to all patients with acute myocardial infarction, it must be proved that even in the milder cases,

the preventable mortality and morbidity significantly exceeds the incidence of complications and death attributable to the drug itself. We have shown that the employment of bishydroxycoumarin could not have prevented more than one death among every 100 patients in our series who sustained a "mild" attack. Moreover, if the drug worked to perfection (and this is certainly not the case) it could avert only eight clinical thromboembolic episodes in every 1000 patients, since this was the total incidence of the complication in our "good risk" group. Against such relatively small benefit involving a considerable expenditure of "time, trouble and money," one must weigh the hazards inherent in any interference with blood clotting. Increasing numbers of case reports are appearing in the literature in which hemorrhagic complications and death have resulted from the use of anticoagulants.[6–9] Sporadic reports of single cases or groups of cases give no assistance in determining the relative frequency of deaths due to bishydroxycoumarin but they do indicate that such results can be encountered by physicians experienced in anticoagulant therapy. The data collected by Nichol[10] summarizing the experience of 136 physicians showed that major bleeding occurred in 2 per cent of approximately 15,500 anticoagulant-treated patients. The mortality rate in this group, from hemorrhage induced by dicumarol or heparin, was 0.18 per cent. Nichol himself encountered major hemorrhage in 10 per cent of 160 patients with acute myocardial infarction to whom he administered bishydroxycoumarin. In our opinion the true death rate and incidence of hemorrhagic complications from anticoagulants will be found to be considerably higher than has been realized, when careful necropsy studies replace "snap" judgment in establishing the cause of death in patients receiving these drugs.

Most of the available statistics concerned with the dangers of anticoagulant therapy reflect the experience of skilled investigators in large medical centers where excellent facilities for prothrombin determination exist. Consideration should be given to the probable results of therapy administered in smaller hospitals or in the patient's home under the guidance of less skilled hands. It must not be overlooked that general practitioners and not "scientific investigators picked for their outstanding reputation in heart disease" treat the vast majority of patients with acute myocardial infarction. Moreover, it is in the milder cases that the general practitioner is likely to have exclusive control without benefit of consultation.

Regardless of the attending physician's skill, however, or the reliability of laboratory facilities, we believe that it is neither necessary nor desirable to administer bishydroxycoumarin to cases of acute myocardial infarction which qualify as "good risks" according to our criteria. The evidence indicates that in such instances, this form of therapy may actually do more harm than good. Bishydroxycoumarin should be employed only in those patients in whom unfavorable prognostic signs are observed. Our statistics indicate that only in such cases is the incidence of clinical thromboembolism and thromboembolic deaths sufficiently high to justify the calculated risk from hemorrhage.

In a recent study[11] it was shown that in the individual case, age has no influence upon immediate survival following acute myocardial infarction. The analysis demonstrates that the clinical picture alone provides the basis for formulating prognosis in any given case. Consequently, age should not be considered an important factor indicating or contraindicating the use of anticoagulants in this disease.

Summary and Conclusions

An analysis of the mortality and incidence of thromboembolism in 1047 cases of acute myocardial infarction treated conservatively shows no justification for the routine employment of bishydroxycoumarin (dicumarol) in this disease. The death rate in 489 "good risk" cases treated without anticoagulants was only 3.1 per cent and the incidence of thromboembolism in the same group was only 0.8 per cent. The preventable mortality under bishydroxycoumarin would have been, at most, only 1.0 per cent in these selected cases. Since such small benefit is more than likely to be

nullified or even overbalanced by complications induced by bishydroxycoumarin, its employment should be reserved for the more serious cases of acute myocardial infarction in which the frequency of thromboembolism justifies the risk entailed in its use.

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Frontal and Sagittal Electrocardiograms of Normal and Hypertensive Subjects during an Experimentally Produced Phase of Lowered Blood Pressure

By JOSEPH BRUMLÍK, M.D., AND CHARLES E. KOSSMANN, M.D.

Reduction of the blood pressure in normal and hypertensive subjects by intravenous pyrogen caused the electrocardiograms to assume a more abnormal configuration as judged by present criteria of electrocardiographic normality. A temporary reduction of the blood pressure by the intravenous administration of tetraethylammonium chloride caused only minor and variable modifications of the electrocardiogram. The results of the experiments as done do not support the concept of strain as applied to certain electrocardiographic abnormalities which occur in the course of hypertension.

PATIENTS with hypertension often have electrocardiograms which are characterized by a high voltage of QRS and deviation of its mean axis to the left, a depression of the S-T segment in leads I, II and V_L, and lowering or inversion of the T wave in leads I, V_L, and sometimes lead II.[1–9] Similar abnormalities and a late RS deflection[6] may be encountered in leads from the left side of the precordium. The changes, particularly in the final ventricular deflections, have been ascribed to cardiac "strain."[10–12] This mechanical interpretation is strengthened by the observation that the abnormalities, particularly in the T wave, sometimes disappear after sympathectomy, or after therapeutic measures which presumably cause a prolonged fall in blood pressure.[13–36]

It seemed proper to investigate the possibility of reversing the electrocardiographic abnormalities found in certain hypertensive patients by lowering the blood pressure acutely. With this in mind, the blood pressure was reduced in hypertensive patients and in normal control subjects by the intravenous injection of typhoid vaccine[37, 38] or of tetraethylammonium chloride (Etamon).* [39]

TECHNIC

In order to prevent the febrile phase of the pyrogenic reaction, the patients who were to receive the vaccine were given 2.4 to 3.6 Gm. of amidopyrine during the preceding 12 hours. Control electrocardiograms were obtained before and after amidopyrine. Triple typhoid vaccine,† 0.1 cc., was given intravenously in the morning with the patient in a basal state. Pulse rate, rectal temperature and blood pressure measured with the ordinary mercury sphygmomanometer were recorded before and for every hour of the first day after the injection of the vaccine with the patient recumbent. Tracings were made when a significant fall in blood pressure occurred, which was usually two to five hours after the injection. The blood pressure generally returned to its control level the next day; occasionally the process took several days. As long as the blood pressure remained low, additional electrocardiograms were obtained, and as a rule a tracing was taken when the blood pressure finally returned to its control level.

In addition, in some patients not under basal conditions the blood pressure was reduced by the intravenous injection of 4 cc. of tetraethylammonium chloride (400 mg.).

Observations using triple typhoid vaccine were made on 15 patients (11 women and 4 men), and on five men with normal blood pressure (tables 1

From the Department of Medicine, New York University College of Medicine, and the Third (N.Y.U.) Medical Division and Adult Cardiac Clinic, Bellevue Hospital, New York.

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* Kindly supplied to us by Parke, Davis, and Co., Detroit, Mich.

† New York City Department of Health Standard Triple Typhoid Vaccine.

and 2, figs. 1, 2, and 3). Observations using tetraethylammonium chloride were made on six patients (four women and two men).

Electrocardiograms of the patients receiving vaccine were recorded with a Hindle all-electric electrocardiograph. Electrocardiograms of patients receiving tetraethylammonium chloride were made with a Technicon cardiograph. Changes in blood pressure with the latter drug are so evanescent that multiple leads must be recorded rapidly, a purpose for which the Technicon instrument is well suited. Even with it, however, it was not possible to make as complete an electrocardiographic survey as in the patients receiving the longer acting pyrogen.

The electrocardiograms recorded were: the standard, the unipolar limb, and the usual six unipolar precordial leads; Arrighi's leads[40] in the sagittal plane*; and the potential of the posterior angle of his triangle. In the experiments with tetraethylammonium chloride only the standard leads and the extremity and precordial potentials could be recorded during the brief action of the drug.

The position of the patient when records were made was either recumbent or sitting in bed, but in any one series was constant. None of the patients was taking digitalis or any other drugs known to affect the electrocardiogram, and none was in cardiac failure.

The areas of electrocardiographic deflections were measured by a special technic. The base line just preceding the P wave of the record was regarded as the reference level. Frequent, minute perforations were made in the record itself, the frequency being dictated by the rapidity of change of contour. With the aid of an Elliott comparator the exact time and height or depth of the perforations were determined, corrections made for inaccuracies of standardization, and the curve redrawn on an enlargement of approximately five times. This method obviated the necessity for making corrections for varying speeds of the electrocardiographic camera. Areas were calculated from simple geometric relationships in the reconstructed curve, each deflection being reduced to triangles and quadrangles. Difficulties were encountered as a result of displacement of the P-R segment which was almost always present, and certain assumptions had to be made occasionally with regard to termination of the T_a (T_p) wave. All QRS deflections were measured from the P-R segment as a base line; the levels of the S-T junction and segment, and of the T wave, were referred to the true isoelectric level (U-P interval).

The angle alpha in the frontal (α) and sagittal (α_s or α^{yz})* planes and the length of the vectors concerned were determined with the aid of Goodman's[42] mechanical adaptation of Carter, Richter, and Greene's chart.[43] The two leads in each plane used for calculations were those which displayed well defined deflections easy to measure.

Results

With Vaccine

A. Normal Subjects (Tables 1 and 2, Fig. 1). In the five normal control subjects there was a mean decrease in systolic pressure of 24 mm. Hg (110 mm. to 86 mm.), and of 15 mm. Hg in diastolic pressure (69 mm. to 54 mm.).

In the frontal plane the length of the *QRS vector* shortened on the average 18.7 per cent [4.8 microvolt-seconds (uvs.)] but changes in direction were slight (fig. 1, open circles and dashed arrows), usually counterclockwise (leftward) with one exception, and the greatest deviation was 13.4 degrees.† In the exception

* In these the first electrode is placed in the left submaxillary region; the second is placed on the back opposite the center of the cardiac silhouette seen by x-ray; and the third on the abdomen 3 or 4 cm. to the left of a point midway between the umbilicus and the symphysis pubis. In this paper the difference in potential between the first two electrodes is labeled I_s (s for sagittal); between the first and third, II_s; and between the second and third III_s. If the triangle thus formed is assumed to be equilateral and lying close to the sagittal plane, then by custom the angle α in this plane (α_s or α^{yz}; the angle made by the sagittal plane vector with the horizontal) is 30 degrees larger than the angle between the mean manifest potential in this plane and the side of Arrighi's triangle regarded as lead I_s.

* See footnote, left column, this page.

† In the coordinate system used in electrocardiography it is well known that the sign of the y axis is the reverse of usual mathematical procedure. Further, an electrical axis with an angle alpha of −10 degrees is regarded as being deviated farther to the left than one with an angle of 0 degrees. This, too, is contrary to the usual terminology of polar coordinates in which the greatest deviation to the left is at 0 degrees. Geometrically a change from 0 in either a clockwise or counterclockwise direction through any part of 180 degrees is really a deviation of the axis concerned to the right of its original position. The electrocardiographic method of nomenclature with regard to the frontal plane, including the unfortunate use of "deviation" for "direction," is so universally used that a change at this time seems undesirable. However, when a mean manifest potential changes its direction in experiments such as reported, the nomenclature often breaks down. For example, it is difficult to say in which direction deviation has occurred, right or left, when the angle α changes from −160 to −120 degrees. The least confusing adjectives to describe deviation in the frontal

(subject Zuc), the angle underwent a change but the vector was small and the direction of change was uncertain. Excluding this case, the average counterclockwise deviation was 4.8 degrees. In four of the five normal subjects the shortening of the QRS vector in the sagittal plane averaged 11.8 per cent (3.5 microvolt-seconds). Deviation in this plane was consistently posterior (counterclockwise) and averaged

plane are clockwise and counterclockwise, and these are used throughout this paper.

In a paper of a similar kind,[45] deviations of the mean manifest potential in the frontal plane were determined from the observer's point of view, that is, to his right or to his left.

With regard to the sagittal plane, any nomenclature adopted is unhampered by precedent or previous usage. In this paper a horizontal axis directed posteriorly as viewed from the left side of the subject is said to display a sagittal angle alpha (α_s) of 0 degrees; when directed anteriorly it is 180 degrees. Deviations away from the former in either direction are forward; deviations away from the latter in either direction are backward. When the deviation of an axis, compared to its original position, is counterclockwise in the sagittal plane viewed from the left the angle of change is preceded by a minus sign (table 1). It is realized that this is also contrary to mathematical usage.

TABLE 1.—*Blood Pressure, Heart Rate, Size and Direction of Vectors for QRS, T, and QRS-T before and after Injection of Intravenous Pyrogen*

Patient	Blood Pressure (mm Hg)		Heart Rate (beats per min.)	Frontal (xy)						Sagittal (yz)					
				QRS		T		QRS-T		QRS		T		QRS-T	
	Syst.	Diast.		A	α	A	α	A	α	A	α	A	α	A	α
5 Normal Subjects (before pyrogen)															
Car	100	60	78	34.6	55.6	32.0	25.0	64.4	41.0	27.6	77.8	37.4	102.6	63.8	92.0
McM	110	78	76	18.6	70.2	27.2	57.2	45.2	62.4	33.6	69.6	19.5	83.8	53.0	74.8
Mos	110	70	82	29.6	68.8	41.2	54.2	70.0	60.1						
Mul	120	70	66	39.0	78.8	35.0	53.0	72.2	66.4	48.8	103.0	30.8	95.4	79.8	100.0
Zuc	110	65	61	6.6	104.7	27.0	30.2	29.5	42.6	8.8	−22.1	41.0	101.0	37.0	89.0
Mean	110	69	73	25.7	75.5	32.5	43.3	56.3	54.4	29.7	63.4	32.2	95.0	58.4	89.0
15 Hypertensive Patients (before pyrogen)															
Bry	142	110	80	44.4	3.0	13.2	58.7	53.0	15.2						
Byr	170	115	72	3.0	46.2	3.5	123.2	5.1	88.2						
Cham	255	170	109	59.0	10.0	42.4	143.0	43.3	55.9						
Chap	275	130	73	62.4	8.8	23.7	−177.0	39.1	12.7						
Del	222	136	83	53.0	−3.8	73.6	169.5	23.6	154.5	33.6	19.0	37.4	−152.0	6.8	−102.2
Did	188	95	58	35.0	30.0	32.2	−51.8	51.1	−9.0						
Get	210	115	69	44.8	−12.0	8.5	112.5	40.3	−1.7	18.0	73.0	10.0	98.8	27.3	82.3
Hol	160	125	70	48.6	1.7	3.0	−10.0	51.7	1.0	25.2	68.2	15.7	162.0	29.0	101.2
Jon	160	90	84	30.0	10.4	25.4	−97.0	32.8	−36.5						
McG	162	92	79	26.3	−26.4	4.4	86.3	25.0	−16.6	15.6	−32.8	5.5	60.0	16.2	−13.4
Orr	244	180	96	41.0	23.5	24.5	96.2	53.7	49.3						
Pae	155	110	69	23.0	68.2	19.9	9.2	37.6	41.9	39.6	62.2	42.0	103.6	76.5	83.6
Pas	160	110	73	31.0	61.3	22.7	133.2	43.7	91.2						
Poe	188	98	78	10.3	64.0	10.5	−3.2	17.5	30.0						
Roo	180	120	74	80.3	13.2	95.2	−172.2	17.0	162.1	52.8	85.8	22.4	−146.3	43.1	110.2
Mean	191	120	78	39.5	19.4	26.8	109.7	35.6	27.9	30.8	40.1	22.2	140.5	33.2	89.2

A is the mean manifest area in microvolt-seconds.

α in degrees. The mean values for α were determined by obtaining the mean of the ratios of the sines to the cosines of the angles.

TABLE 1.—*Continued*

Patient	Blood Pressure (mm Hg)		Heart Rate (beats per min.)	Frontal (xy)						Sagittal (yz)					
				QRS		T		QRS-T		QRS		T		QRS-T	
	Syst.	Diast.		A	α	A	α	A	α	A	α	A	α	A	α
5 Normal Subjects (after pyrogen)															
Car	60	45	107	25.6	42.4	9.9	8.9	34.5	33.0	40.0	58.4	5.6	90.8	45.2	62.6
McM	84	56	84	22.4	60.3	9.9	−19.9	25.9	38.1	23.3	29.8	5.2	66.9	27.8	36.4
Mos	100	62	105	26.8	69.8	38.4	−37.2	39.7	3.2						
Mul	100	60	106	25.6	81.0	8.8	3.2	28.8	63.5	34.2	90.0	9.8	72.0	43.5	85.9
Zuc	85	45	82	4.2	−98.0	8.6	19.8	7.6	−9.3	7.3	−30.8	11.0	78.0	11.1	39.4
Mean	86	54	97	20.9	57.2	15.1	−18.4	27.3	25.7	26.2	39.3	7.9	76.9	31.9	55.9
15 Hypertensive Patients (after pyrogen)															
Bry	95	75	96	25.0	9.3	17.6	−134.8	14.8	−35.0						
Byr	130	100	95	3.7	−7.2	2.5	113.5	4.9	18.5						
Cham	184	136	133	86.0	−4.2	49.8	−162.2	44.2	−29.7						
Chap	190	90	90	88.0	−8.8	9.2	−155.2	80.4	−12.5						
Del	174	106	76	56.4	−13.8	72.9	−164.1	36.8	−114.0	28.0	11.2	31.2	−152.8	8.7	−92.6
Did	122	68	88	33.2	53.3	24.2	−128.2	9.0	57.6						
Get	100	65	90	64.4	−6.3	34.6	−175.0	31.3	−18.7	7.4	96.8	12.0	−178.0	14.7	151.9
Hol	120	100	123	37.2	28.6	22.1	−108.8	25.7	−6.6	24.3	77.0	15.0	−144.0	16.5	113.6
Jon	125	80	104	35.4	12.5	31.2	−164.4	2.3	−31.5						
McG	135	68	96	19.3	−18.4	22.3	−155.0	15.5	−95.8	13.9	−17.8	22.4	−100.5	28.0	−70.8
Orr	150	110	107	49.6	58.0	9.6	128.8	51.3	62.9						
Pac	125	80	107	34.0	83.0	20.5	30.1	49.2	63.7	46.0	63.8	18.8	110.2	60.3	76.8
Pas	115	70	99	33.0	95.0	19.5	−94.5	14.2	107.7						
Poe	130	80	100	11.5	66.5	9.4	−10.0	16.6	32.9						
Roo	106	74	85	90.4	13.8	74.0	−160.0	10.6	−11.1	33.6	71.2	26.2	−155.0	24.5	122.7
Mean	133	87	99	44.5	22.4	27.9	−156.6	27.1	0.7	25.6	25.5	20.9	−159.5	25.5	135.8

24.1 degrees.* Changes in length and direction of the QRS vector in either plane were not statistically significant (table 2). Little change occurred in the QRS of the precordial leads.

The *gradient* (QRS-T) in the frontal plane shortened in all, averaging approximately half its control size (fig. 2). It deviated consistently in a counterclockwise direction (mean deviation 28.7 degrees). In the sagittal plane shortening also occurred, averaged 26.5 microvolt-seconds, or slightly less than half its average control value. It also deviated posteriorly (counterclockwise) on the average by 33.1 degrees.

As expected under such circumstances the mean T vector in the frontal plane shortened by 53.5 per cent, and also deviated in a counterclockwise direction by 61.7 degrees (fig. 3). In the sagittal plane the shortening was 75.5 per cent, and the deviation posteriorly (counterclockwise) was 18.7 degrees.

These modifications were all statistically significant ($p < 0.01$) or probably significant ($p < 0.05$) with the exception of the change in direction of the gradient (QRS-T) in the frontal plane (table 2).

These changes in vectors manifested themselves most clearly in the usual clinical leads as

* This mean difference was obtained by calculating the means of the ratios of the sines and cosines of the angles before and after pyrogen and measuring the difference. This is the figure shown in table 1. To calculate standard deviations, however, the ordinary mean of individual differences in the angle was used (table 2). If the vector remained in the same quadrant after the pyrogen, the mean difference obtained by the two methods was identical (table 2).

modifications in the T wave. These consisted usually of a lowering of this deflection in leads II and III with or without a depression of the S-T junction. In the extremity leads a reciprocal change occurred in the T wave in leads aV_L and aV_F with an increase in positivity of the former and a decrease in positivity of the latter during the inscription of this deflection. In the precordial leads there was most often little change in the T wave, but in the exceptions (figs. 4 and 5) the T wave became deeper or inverted in leads further to the right than was the case before the pyrogen was given.

It was deduced from these observations in normal subjects that the spatial QRS vector was changed insignificantly in size following the use of pyrogen. The decrease in length of its frontal projection was in part the result of its posterior deviation. The shortening of the spatial vector representing the ventricular gradient was distinctly not on the basis of a change in position alone since a decrease in its size occurred in convincing degree in both the frontal and sagittal planes. The conclusion seemed justified, in accordance with current theory, that the differences in the duration of the excited state in different parts of the normal ventricular muscle were reduced by intravenous pyrogen as given. These conclusions seemed to be valid even when allowances were made for the probable inaccuracies which result from the use of Arrighi's triangle for measurement of the sagittal components of the vectors measured.

TABLE 2.—*Mean Differences in Blood Pressure, Heart Rate, QRS, T, and QRS-T Produced in Normal and Hypertensive Subjects by Intravenous Pyrogen*

	Bl. Press.		Ht Rate	Frontal (xy)						Sagittal (yz)					
				QRS		T		QRS-T		QRS		T		QRS-T	
	S	D		A	α	A	α	A	α	A	α	A	α	A	α
5 Normal Subjects															
Before Pyrogen	110	69	73	25.7	75.5	32.5	43.3	56.3	54.4	29.7	63.4	32.2	95.6	58.4	89.0
After Pyrogen	86	54	97	20.9	57.2	15.1	−18.4	27.3	25.7	26.2	39.3	7.9	76.9	31.9	55.9
Difference ($\bar{x}$)	*−24*	*−15*	*24*	*−4.8*	*−5.0**	*−17.4*	*−48.9**	*−29.0*	*−28.7*	*−3.5*	*−20.2**	*−24.3*	*−18.7*	*−26.5*	*−33.1*
% Change	−21.8	−21.7	32.9	−18.7	—	−53.5	—	−51.5	−52.8	−11.8	—	−75.5	−19.5	−45.4	−37.2
Stand. Dev. (S)	10.8	6.1	11.6	6.6	7.7	8.8	38.7	11.2	24.9	11.9	14.4	8.4	5.5	7.3	14.7
Stand. Error ($S_{\bar{x}}$)	4.85	2.71	5.17	2.96	3.86	3.94	17.25	5.00	11.11	5.95	7.16	4.20	2.76	3.65	7.34
t observed	4.948	5.535	4.642	1.621	1.372	4.416	2.835	5.800	2.592	0.586	2.809	5.786	6.605	7.760	4.482
t (p=0.01)	4.604	4.604	4.604	4.604	5.841	4.604	4.604	4.604	4.604	5.841	5.841	5.841	5.841	5.841	5.841
t (p=0.05)	2.766	2.766	2.766	2.766	3.182	2.766	2.776	2.766	2.776	3.182	3.182	3.182	3.182	3.182	3.182
15 Hypertensive Patients															
Before Pyrogen	191	120	78	39.5	19.4	26.8	109.7	35.6	27.9	30.8	40.1	22.2	140.5	33.2	80.2
After Pyrogen	133	87	99	44.5	22.4	27.9	−156.6	27.1	0.7	25.6	25.5	20.9	−159.5	25.5	135.8
Difference	*−58*	*−33*	*21*	5.0	4.2*	1.1	4.2*	−8.5	−12.3*	−5.2	4.4*	−1.3	−1.3*	−7.7	3.41*
% Change	−30.4	−27.5	26.9	12.7	—	4.1	—	−23.9	—	−17.2	—	−5.9	—	−23.2	—
Stand. Dev. (S)	24.6	15.3	13.2	12.8	22.6	13.1	51.8	18.8	46.4	8.2	14.3	13.2	7.7	11.9	41.3
Stand. Error ($S_{\bar{x}}$)	6.22	3.96	3.43	4.73	5.84	3.38	14.68	4.86	12.38	3.35	5.85	5.40	4.42	4.87	16.86
t observed	9.374	8.333	6.474	1.057	0.720	0.299	0.286	1.750	0.997	1.580	0.756	0.241	0.296	1.715	0.202
t (p=0.01)	2.977	2.977	2.977	2.977	2.977	2.977	3.106	2.977	3.012	4.032	4.032	4.032	9.925	4.032	4.032
t (p=0.05)	2.145	2.145	2.145	2.145	2.145	2.145	2.201	2.145	2.160	2.571	2.571	2.571	4.303	2.571	2.571

Blood pressure in mm. Hg.
Heart rate in beats per minute.
A is the mean manifest area in μvs.
α in degrees.
— means a decrease in size or deviation in a counterclockwise direction when used with values for "Difference" or "% Change".
* These are means of individual differences in angle alpha, not the difference between mean angles. They cannot be expressed as a percentage change.
Italic differences are statistically significant or probably significant.

Hypertensive Patients (tables 1 and 2). In the 15 patients there was a considerable fall in blood pressure, following the pyrogen, which averaged 58 mm. Hg systolic (191 mm. to 133 mm.), and 33 mm. Hg diastolic (120 mm. to 87 mm.).

In the frontal plane the length of the *QRS* vector varied greatly after pyrogen (fig. 1, solid

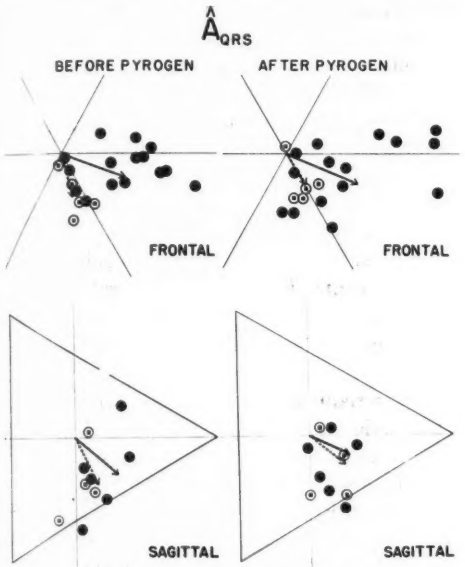

FIG. 1. *Mean manifest area of QRS ($\hat{A}_{QRS}$) in the frontal (Einthoven) and sagittal (Arrighi) planes before and after reduction of the blood pressure by intravenous pyrogen in normal and hypertensive subjects.* In this and the following two figures (figs. 2 and 3) the heads of the individual vectors are designated by an open circle for the normal subjects and by a solid circle for the hypertensive patients. The mean size and direction of all the vectors of the normal subjects is represented by a broken arrow; of the hypertensive patients by a solid arrow. The mean of the angle alpha was obtained in each group by taking the mean of sines and of the cosines of each angle. The ratio of these means gave the tangent of the mean angle alpha. Insignificant changes in size and direction are observed to occur in both planes (see tables 1 and 2).

circles and arrows). The range was between an increase of 27.0 microvolt-seconds and a decrease of 19.4 microvolt-seconds (table 1). The average change was an increase of 5.0 microvolt-seconds or 12.7 per cent. The angle alpha in control records ranged from +68.2 degrees to −2.4 degrees; only three patients displayed an angle alpha less than 0 degrees. After pyrogen the change in direction was quite variable but in 11 of the 15 it was clockwise (to the right); but in all the average change in this direction was only 3.0 degrees. However, in one instance it changed in the opposite direction by 53.4 degrees.

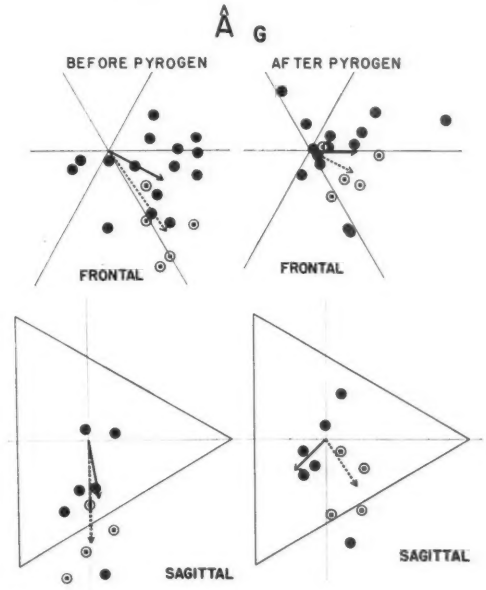

FIG. 2. *Mean manifest area of QRS-T ($\hat{A}_G^1$) in the frontal and sagittal planes before and after reduction of the blood pressure by intravenous pyrogen in normal and hypertensive subjects.* In both groups and in both planes the mean vector is shorter after pyrogen. In the frontal plane both rotate slightly in a counterclockwise manner; in the sagittal plane the mean vector of the normal subject (dashed arrow) rotates counterclockwise (backward viewed from the left) but the mean vector of the hypertensive patients (solid arrow) changed its direction in the opposite way, that is, forward. Changes in the length and direction of the mean normal vector are probably significant ($p < 0.05$) with the exception of the change in direction in the frontal plane (table 2). Changes in the length and direction of the abnormal (hypertensive) mean vector are statistically insignificant.

Observations in the sagittal plane were available on six subjects. In five of the six the QRS vector shortened and the mean shortening was 5.2 microvolt-seconds (17.2 per cent). The mean change in direction was backward (counterclockwise) by 14.6 degrees (fig. 1).

None of the changes in the length or direction of the QRS vector was statistically significant (table 2).

A moment's reflection on these mean values of QRS length and direction indicates that they are not likely, assuming that the true frontal and sagittal values of the vectors are given by

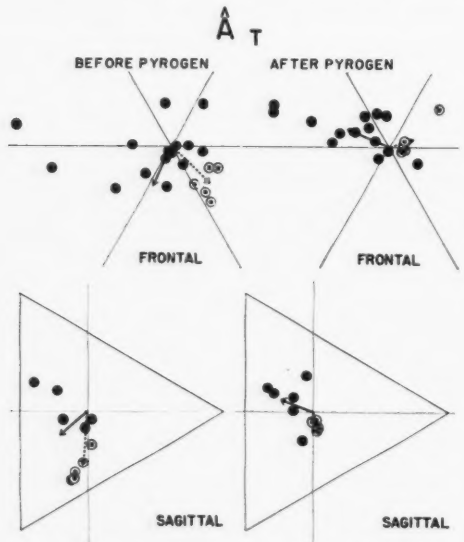

FIG. 3. *Mean manifest area of T ($\hat{A}_T$) in the frontal and sagittal planes before and after reduction of the blood pressure in normal (open circles, dashed arrow) and hypertensive (solid circles, solid arrow) subjects.* The mean vector of the hypertensive patients changed little in size in either plane after pyrogen. The normal mean vector shortened in both. Rotation of the two vectors after pyrogen was in opposite directions in the two planes—counterclockwise for the normal, clockwise for the hypertensive. Only the changes in size and direction of the mean normal vector are probably significant ($p < 0.05$). Failure of a single spatial vector to account for the frontal and sagittal projections can be seen best in this figure (dashed arrow, after pyrogen). Poorest fits were obtained in individual cases when the vector was of small size as in this instance of the mean normal vector (see text).

Einthoven's and Arrighi's triangles. The reason is as follows: An assumed decrease in length of the spatial QRS vector will cause an increase in the length of its frontal projection only if its change in direction in the sagittal projection is toward the vertical. In this instance the mean change in sagittal direction was the reverse, that is, toward the horizontal. A further analysis of the records of the six patients under consideration revealed that only two displayed changes in the frontal and sagittal QRS vectors which could fit a single change in the spatial vector. This was in contrast to what was observed in the normal group. The observation is significant in that conclusions with regard to the spatial vectors in hypertensive patients must be tentative, and absolute statements can be made with regard to these vectors only as studied by Einthoven's and Arrighi's triangles. A final solution of the problem revolves about the choice of a reference system which will yield the frontal and sagittal components of the mean manifest potential of any deflection accurately.

The *gradient* in the frontal plane showed an average shortening of 8.5 microvolt-seconds (23.9 per cent). There was considerable scatter in the distribution (fig. 2) although 11 of the 15 showed shortening. In the sagittal plane the change in direction in both planes after pyrogen was so variable as to make mean values in this small series relatively meaningless. However, the trend (fig. 2) was counterclockwise in the frontal plane and clockwise in the sagittal plane, the latter being the opposite of what occurred in the normal subjects. In terms of the direction of the spatial gradient the average change was from a direction downward, to the left, and backward to a direction horizontal, to the left, and forward. It is to be noted in figure 2 that the average vectors in the two planes either before or after pyrogen cannot have their origin from a single spatial vector as in the case of the QRS vector.

With regard to the length of the spatial gradient the trend was, as in the normal subjects, toward a reduction but to a lesser degree (fig. 2, table 2).

The *T vector* in the frontal plane, as could be deduced from the change in the gradient, was quite variable but the mean change in length was small (+1.1 microvolt-seconds, +4.1 per cent). In the sagittal plane the mean change in length was also slight (−1.3 microvolt-seconds, −5.9 per cent). Little can be said about the change in direction in either plane because this varied widely, but the trend of the spatial T vector after pyrogen was from a direction do wn-

ward, to the right, and forward, to upward, to the right and forward (fig. 3). None of these changes in length or direction was statistically significant (table 2).

These changes in vectors manifested themselves most clearly in the usual clinical leads as electrocardiograms which were the least abnormal. In the so-called "typical" records of hypertension the changes during the hypotensive phase were not so obvious (figs. 4 and 5), although measurements of areas proved that they had occurred (table 1).

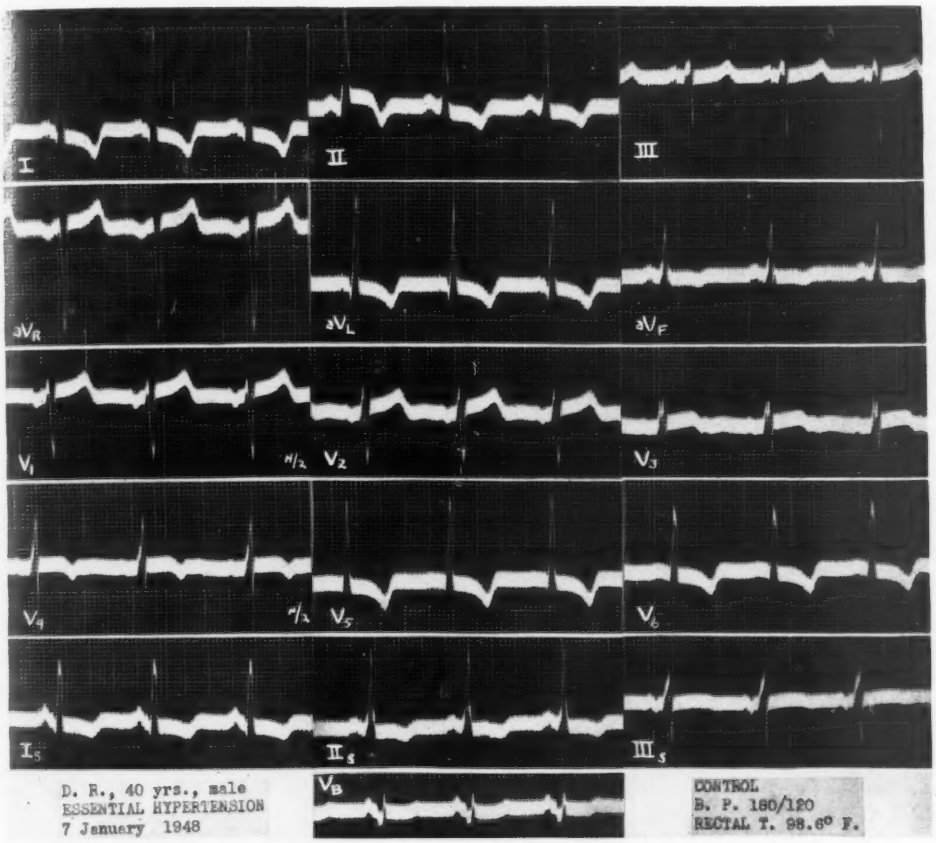

FIG. 4. *Patient, D. R., essential hypertension. Before pyrogen.* The standard leads (I, II, III), the augmented extremity potentials (aV_R, aV_L, aV_F), the sagittal leads of Arrighi (T_S, II_S, III_S), and the potential of the point on the back (V_B) used in recording the sagittal leads were made with the string sensitivity normal (1 mv. = 1 cm.). The precordial leads (V_1, V_2, V_3, V_4, V_5, V_6) were recorded with the string sensitivity at half normal (1 mv. = 0.5 cm). Time lines occur every 0.04 second. Ventricular rate is 73 beats per minute.

a modification in the T wave. In general it became lower in lead I, higher in lead III. In no instance did an originally inverted T wave in lead I become upright. The S-T junction remained unchanged or was slightly depressed. Variations in the S-T segment and T wave were most apparent in those patients with control

From the extremity potentials it was evident that clockwise rotation of the QRS axis in the frontal plane, when it occurred, caused an increase in the size of the R wave and a decrease in the size of the S wave in lead aV_F, and the reverse events in lead aV_L. The usual depression of the S-T segment and decrease in

size or inversion of the T wave in lead I was produced by an increase in potential of the right arm and a simultaneous decrease in the potential of the left arm during the inscription of these deflections.

The precordial leads usually displayed no change in the form or size of the QRS deflections. Readily apparent modifications of the final ventricular deflections, particularly in leads from the left side of the precordium, were similar to what was observed in lead I. The change in direction of the spatial T vector was accompanied sometimes by inversion of the T wave in precordial leads farther to the right than observed in the control records.

With Tetraethylammonium Chloride

The results of injecting tetraethylammonium chloride intravenously in six hypertensive subjects were variable and surprisingly minor in nature. The only consistent change was a diminution in the size of the R wave in leads I and II. The most striking change seen in one of these patients was in the form of the S-T segment and T wave without any important quantitative change in these deflections. In two pa-

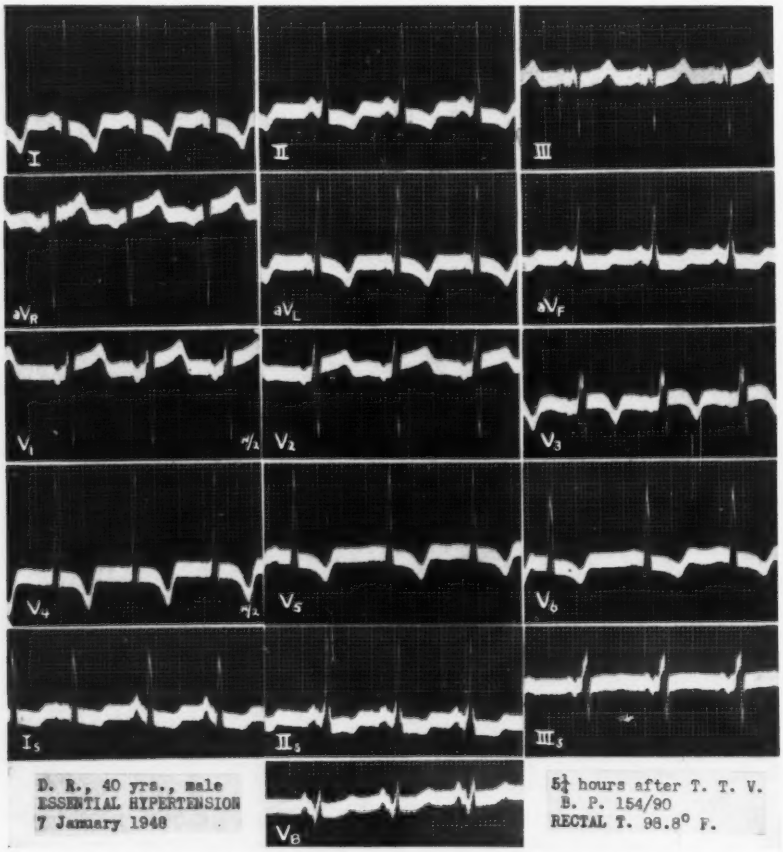

FIG. 5. *Patient D. R., essential hypertension. After pyrogen.* The ventricular rate is 91 beats per minute. The most obvious gross change is the deep inversion of the T wave which has occurred in leads V_3 and V_4, and the change to upright of the T wave in lead V_8. Symbols and time lines are as in figure 4.

tients the S-T segment in leads I and II was slightly depressed and in two it was slightly elevated during the hypotensive phase.

The impression gained was that the drug as used had no distinct or consistent effect on the form of the electrocardiogram although the blood pressure was always reduced appreciably (mean change from 176 to 127 mm. Hg systolic and 100 to 74 mm. Hg diastolic).

Discussion

The electrocardiographic changes observed during the phase of hypotension following triple typhoid vaccine in normal and hypertensive subjects are similar to those described by Freedberg, McManus and Altschule[45] during fever induced in normal subjects. Although fever was not always prevented entirely by premedication with amidopyrine, the temperature never rose to levels which are usually attained with the dosage of vaccine employed. Furthermore, there was no correlation between the extent of the electrocardiographic changes and the extent of the fever, and the same type of changes occurred whether fever was entirely prevented or not. Often the electrocardiographic modification persisted after the temperature subsided. For all these reasons it is believed that the changes reported were not due to fever, or at least not to fever alone.

The injection of the vaccine was followed invariably by a moderate but statistically significant rise in the heart rate (tables 1 and 2). In spite of the fact that an increase in the sinus rate has, as Ashman has shown,[46, 47] a bearing upon the form of the electrocardiogram, the changes observed in our series by far exceeded those usually attributed to higher rates. They also persisted, or were even greater, after the rate returned to control values.

An explanation for the electrophysiologic phenomena observed is difficult. The pyrogen causes such changes as a decrease in peripheral resistance, a fall in intraventricular and intramural ventricular pressure, a decrease in tension in the aortic wall with possible modification of suspension of the heart in the thorax, a change in coronary blood flow, and a variety of alterations in the physicochemical composition of the blood.[48] Although a majority of these depend on a fall in blood pressure, it cannot be stated with certainty that the alterations observed in the electrocardiograms were caused exclusively by this variable. However, as long as the blood pressure remained low, the deviations persisted.

Since the electrocardiogram in the hypertensive patients was modified by a relatively sudden and brief fall in blood pressure in a direction which by present standards may be regarded as more "abnormal," the question arose whether a reduction of blood pressure is the factor responsible for the reverse modifications which have been reported to occur after sympathectomy. A good many records have been

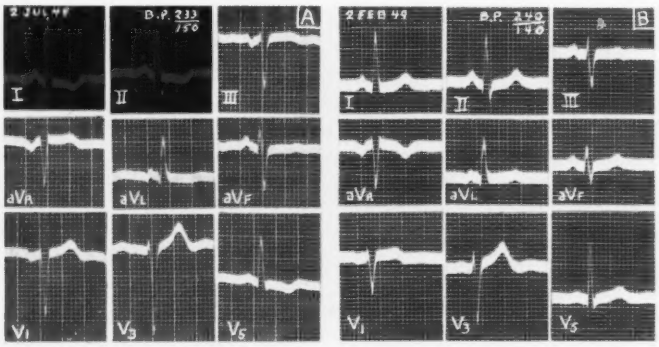

Fig. 6. Electrocardiograms (I, II, III, aV_R, aV_L, aV_F, V_1, V_3, V_5). before (*A*) and 6 months after (*B*) bilateral lumbosacral sympathectomy. Although the blood pressure is almost identical there is a complete reversion of the T waves to what is regarded as normal.

published showing a return of T waves to "normal" after sympathectomy,[12–28] but none, except those quoted by Raab and Lepeschkin,[49] have demonstrated an "improvement" in the electrocardiogram after sympathectomy without a fall in blood pressure. We have had the opportunity of observing* one such case which is summarized in figure 6. A record made on July 2, 1948 displayed distinct abnormalities of the T wave in leads I, II, aV_L, V_5 and V_6 (not shown) at a time when the blood pressure was 233/150. A sympathectomy was done in two stages on July 28 and August 4. Another record made on Aug. 21, 1948 (not shown) when the blood pressure was 150/100 showed a partial regression of these T-wave abnormalities. A record made on Feb. 2, 1949 (fig. 6) displayed complete disappearance of the abnormal T waves but the blood pressure was 240/140, its approximate preoperative level. The ventricular rates in the first and last records were 66 and 72 respectively, and the frontal axis and area of QRS was similar in both.

The case is cited in support of the experimental data given. Together they seem to indicate that variables other than the fall in blood pressure can be responsible for those alterations in ventricular regression which result in more "normal" T waves in the electrocardiogram of certain hypertensive subjects when the hypotension is induced by sympathectomy,[12–28] diet,[29–33] or other means. Further, certain theoretic considerations permit the conclusion that an upright T wave in lead I, or lead V_L when there is considerable hypertrophy of the left ventricle, may actually represent a more abnormal electrophysiologic state than an inverted T wave in these leads.

The trend of the frontal QRS-T in our experiments was to shorten and rotate to the left (counterclockwise) in the frontal plane (fig. 2). These findings are somewhat at variance with the observations made on preoperative and postoperative electrocardiograms by Boyer and Hewitt[50] in 106 hypertensive patients subjected to sympathectomy (Smithwick). In their series the mean manifest potential of QRS and of QRS-T shifted to the right (clockwise) but only in the former was the change statistically significant.

* Initial observations were made by Dr. Ignacio Chavez of Mexico City, to whom the authors are deeply indebted for permission to use his data.

Summary and Conclusions

1. Regarding QRS, T, and QRS-T as vectors studied in two planes by means of Einthoven's and Arrighi's triangles, the specific modifications which occurred after intravenous triple typhoid vaccine were:

(a) In five normal subjects the QRS-T shortened and rotated in a counterclockwise manner in the frontal plane, and shortened and rotated posteriorly (counterclockwise viewed from the left) in the sagittal plane. These modifications in the ventricular gradient were reflected best in the similar behavior of the T vector; the QRS vector was modified similarly but to an insignificant degree.

(b) In 15 hypertensive patients the QRS-T vector also shortened in both planes but changes in direction were quite variable. On the average, the change in direction was counterclockwise in the frontal plane but clockwise (viewed from the left) in the sagittal plane. The mean changes in size and direction of all vectors in these 15 patients were statistically insignificant.

2. Intravenous pyrogen reduces the size of the differences in the duration of the excited state in the ventricular muscle both in normal subjects and in hypertensive patients but to a lesser degree in the latter. The fall in blood pressure caused by the pyrogen is probably but not absolutely the important variable concerned with this change.

3. The modifications in the ventricular gradient produced by intravenous triple typhoid vaccine resulted in electrocardiograms with a more "abnormal" configuration, particularly of the T wave.

4. The electrocardiographic response of six hypertensive subjects to temporary hypotension produced by tetraethylammonium chloride given intravenously was minor and variable, except for the consistent shortening of the QRS vector as measured in the frontal plane only.

5. Attention is called to the tentative va-

lidity of some of the data by virtue of the disclose unreliability of the methods used to obtain the exact spatial vector.

6. Electrocardiograms of a hypertensive patient are presented in which the T waves returned to "normal" following a sympathectomy only after the blood pressure had returned to preoperative hypertensive levels.

7. The experimental data presented and the cases cited do not support the concept of "strain" as applied to certain electrocardiographic abnormalities in hypertension which are sometimes reversed by agents or procedures which decrease the blood pressure.

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Congenital Aneurysmal Defect of the Membranous Portion of the Ventricular Septum

Associated with Heart Block, Ventricular Flutter, Adams-Stokes Syndrome and Death

By Richard J. Clark, M.D., and Paul D. White, M.D.

A case of congenital aneurysmal defect of the ventricular septum is reported which appears to be unique in that this lesion was the only significant finding at autopsy. The patient had evidence of auriculoventricular block for a period of 26 years, at first partial and then complete. She succumbed at the age of 47 to a series of Adams-Stokes attacks which were demonstrated to be set off by paroxysmal ventricular flutter followed by ventricular tachycardia and ventricular standstill. Pertinent literature is briefly reviewed.

THE FOLLOWING case is considered worthy of recording since it appears to be the only one which we can find on record where an aneurysmal defect of the ventricular septum was the sole significant anatomic lesion found at autopsy. It demonstrates that ventricular flutter, unsuspected without cardiographic evidence, may precipitate the Adams-Stokes type of syncope.

Previous Literature

Aneurysm of the Ventricular Septum. Because of its presumed lack of clinical significance, little has been written on the subject of aneurysm of the ventricular septum. Abbott, in Osler's Modern Medicine,[1] described the pathologic condition briefly and reviewed the original studies of Mall.[2] In 1938 Lev and Saphir[3] published two cases and reviewed 70 cases which had been reported in the literature. Since this review we find only one further case reported, that of Castoldi[4] in 1942.

Adams-Stokes Syndrome. The Morgagni-Adams-Stokes syndrome as originally described referred to the association of syncope, epileptiform convulsions and marked slowing of the heart action. Parkinson and co-workers[5] in 1941 reviewed all reported cases of the Adams-Stokes syndrome with electrocardiographic tracings and found that only 55 per cent of reported attacks were associated with ventricular arrhythmias. Parkinson defined the Adams-Stokes disease as the "name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation or a combination of these." Schnur,[6] in 1948 reiterated these views and presented a case of ventricular fibrillation, tachycardia and asystole imposed upon complete heart block. Pastor and Worrilow[7] have recently reviewed the electrocardiographic patterns in the Adams-Stokes syndrome and found 20 cases on record in which both ventricular arrhythmias and ventricular standstill had been shown to occur during the Adams-Stokes syncope; in eight of these cases the arrhythmias were in association with complete A-V block.

Congenital Heart Block. Heart block of congenital origin as reported in the literature has been reviewed by Yater and associates,[8] with a study of 44 acceptable cases of which a ventricular septal defect was found to be present in 26. Faessler[9] reported eight cases of the Adams-Stokes syndrome associated with congenital heart disease, of which six were diagnosed as having ventricular septal defects. Essentially all types of congenital defects have been reported as associated with heart block.[10]

Ventricular Flutter versus Fibrillation. In 1925

From the Cardiac Department, Winchester Hospital and the Cardiac Clinics and Laboratory of the Massachusetts General Hospital, Boston.

Sir Thomas Lewis[11] stated that the nature of the disturbances included under the term ventricular fibrillation was undefined. He believed that varying grades of ventricular arrhythmias occurred, as in the auricles, ranging from flutter, to impure flutter and grossly impure flutter or fibrillation. Fastier and Smirk[12] described the condition of ventricular flutter, observed in experimental cats and dogs, as showing characteristic regular undulatory waves on the electrocardiogram which are quite in contrast with the disorganized movement, usually of smaller amplitude, seen in ventricular fibrillation.

Case History

S. B., aged 47. This patient was said to have been in normal health, except for diphtheria in childhood, until 1921, when, at the age of 21, she was delivered of her first and only child. A review of her hospital record indicated that following a normal labor and delivery she had had five fainting spells followed by a convulsion, associated with irregularity of the pulse which at times was not palpable. By the patient's own statement, her pulse subsequent to this was usually slow, about 40 per minute, but she was generally well and led a normal life. In 1936 a careful examination showed a pulse rate of 44, a blood pressure of 136/80, with heart sounds of good quality. An electrocardiogram showed first degree A-V block with a ventricular rate of 42 and a P-R interval of 0.24 of a second; the tracing was otherwise not remarkable.

In March 1947, at the age of 47, the patient was seen in consultation by one of us (R. J. C.). For the previous four or five years she had complained of "dizzy sensations," distinct increase in dyspnea and brief bouts of low substernal pressure with radiation to the left arm brought on by excitement or exercise. Examination showed a pulse rate of 48, regular and full. The blood pressure was 165/100. The heart showed a left border of dullness 2 cm. outside the midclavicular line. The heart sounds were forceful in character with an accentuated pulmonary second sound which was greater than the aortic second sound. There was a grade 2 systolic murmur, without a thrill, heard best between the apex and the left sternal border. The lungs were clear and there was no evidence of congestive failure. Fluoroscopic examination showed a slight increase in the transverse diameter of the heart with the appearance of slight left ventricular hypertrophy. An electrocardiogram showed a regular ventricular rate at 42 with the P-R interval increased to 0.26 of a second, but was otherwise not remarkable. A urinalysis was normal. A Hinton test was negative. Photoelectric determination of hemoglobin was 13.5 Gm. The presumptive diagnosis at that time was congenital heart disease with a ventricular septal defect and associated heart block with superimposed coronary artery disease.

On the morning of June 15, 1947, the patient was admitted as an emergency case to the Winchester Hospital because of an attack of generalized convulsions and unconsciousness of 10 minutes duration. Directly after admission a recurrent attack was observed. The pulse could not be obtained and no heart sounds were heard. One-half cc. of 1:1000 adrenaline solution was given intramuscularly. Another attack occurred after a half hour, during which an electrocardiogram was obtained. This showed ventricular flutter at a rate of 220 in the portion taken during the acute attack. This was followed by complete A-V block with an auricular rate of 130 and a ventricular rate of 42, also variable ectopic ventricular beats. The basic pattern had not otherwise changed significantly from that found in March.

When it became apparent that the true situation was one of Adams-Stokes episodes associated with ventricular flutter, adrenaline was omitted and the patient was started on quinidine sulfate by mouth and atropine sulfate, 0.6 mg. by hypodermic injection. During the afternoon she continued to have convulsions at approximately hourly intervals; frequently clusters of two or three attacks covered a period of 15 to 20 minutes. On several occasions, between attacks, the patient complained of severe substernal oppression with radiation to the left arm wherefore morphine sulfate 10.6 mg. by hypodermic was given. She was maintained in an oxygen tent. The patient was seen in consultation by one of us (P.D.W.) that afternoon. Quinidine sulfate was stepped up in dosage from 0.2 Gm. orally to 0.4 Gm. of lactate every two hours intramuscularly because of vomiting. During the night the patient's attacks decreased slightly in frequency but the following day at 12:30 P.M. there was a more severe seizure in which she expired. During her period of hospitalization the patient had some 30 convulsive seizures. In the course of 24 hours she received 3.5 Gm. of quinidine.

Numerous electrocardiographic observations were made which showed periods of ventricular flutter lasting up to three minutes, frequently followed by periods of ventricular tachycardia lasting two or three seconds, followed by periods of ventricular standstill with P waves decreasing in frequency. The longest period of measured standstill was 75 seconds. Following the ventricular standstill the patient resumed complete heart block with the ventricular rate speeded to about 60 at first then dropping into the 40's. Figure 1 shows a recording of one of the more severe episodes.

The clinical diagnosis prior to autopsy was acute myocardial infarction imposed upon coronary arteriosclerosis disease, with possible congenital heart block.

Pathologic Examination

An autopsy was performed by Doctors Donald McIlvay and Donald A. Nickerson. Significant findings were limited to the heart, which weighed 350 Gm. The pericardium was smooth and glistening. The epicardium was smooth. The coronary arteries were thin walled and patent throughout. The right auricle appeared dilated. The myocardium of the left ventricle was firm and red brown, showing no evidence of fibrosis or infarction; it measured 1.5 cm. in thickness. The right ventricular myocardium was slightly softer but otherwise not remarkable; the wall of the right ventricle measured 0.4 cm. in thickness. The membranous portion of the interventricular septum was paper thin and herniated into the right ventricle, forming a pouch with its mouth on the left ventricular side (fig. 2). The mouth of the pouch measured 1.8 cm. in diameter. The membrane was fused with the medial cusp of the tricuspid valve. The pouch, when ballooned out with the finger, almost completely filled the orifice of the tricuspid valve. The remainder of the valves showed thin delicate leaflets with no evidence of inflammation. The chordae tendineae were normal. Apart from the interventricular aneurysmal defect there were no congenital malformations of the heart or great vessels. The aorta was thin walled, elastic and lined by a smooth velvety intima. Microscopic sections taken from the right and left ventricular musculature showed no recognizable abnormality of

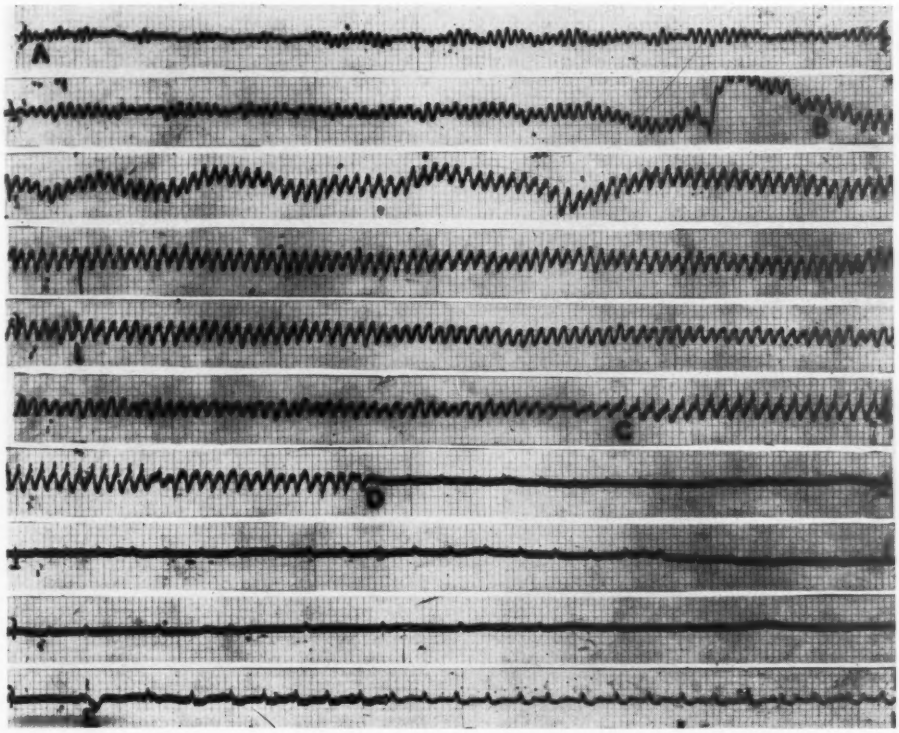
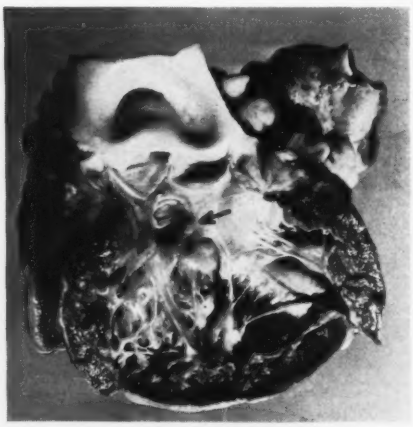


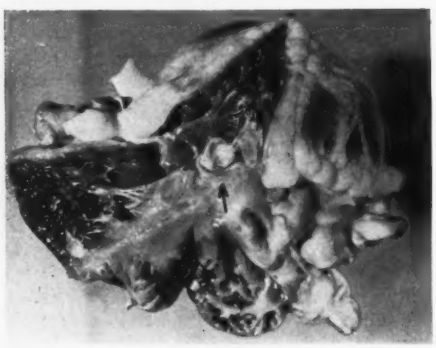
FIG. 1. Continuous electrocardiographic tracing, lead II, taken during a severe convulsive episode. *A*. Onset with ventricular "flutter" at rate of 220. *B*. Widening of the beam caused by severe convulsing and necessity of holding the patient. *C*. Shift to ventricular tachycardia at slower rate again followed by a brief reversion to "flutter." *D*. Appearance of ventricular standstill with only P waves in evidence, with progressive slowing of auricular activity. *E*. Resumption of ventricular activity (escape) with sinus bradycardia followed by high grade auriculoventricular dissociation. Note the disappearance of wide beam shadow as convulsive movements cease. Time intervals equal 0.04 second.

muscle fibers or blood vessels. There was a moderate degree of passive congestion in the lungs, liver, kidneys and spleen. No specific cause of death was found anatomically.

Subsequently more detailed study of the heart was carried out in the Pathological Laboratory of the Massachusetts General Hospital by Doctors David Freiman and Robert Scully. Block sections



A



B

FIG. 2*A*. Aneurysmal defect, as viewed from the left ventricle, located in the membranous septum directly below the aortic valves. *B*. Aneurysmal pouch as viewed protruding into the right ventricle, showing adhesions to the tricuspid valve.

were made of the entire aneurysm. These sections failed to show evidence of anything which looked convincingly like the Bundle of His. The pouch was composed of relatively acellular collagenous tissue. No evidence was found of mural endocarditis.

DISCUSSION

The diagnosis of aneurysmal defect of the ventricular septum cannot be made clinically. In this case historical evidence pointed strongly to the existence of heart block since at least the age of 21 years probably with Adams-Stokes syncope occurring following childbirth. A respite of 26 years without further occurrence is remarkable. The "dizzy spells" which this woman had experienced for about four years were doubtless a result of her heart block. The history pointed strongly toward coronary insufficiency with mild angina pectoris in a woman with early hypertension, yet no coronary disease was found at autopsy. One might speculate as to whether her heart block could have produced a relative coronary insufficiency giving rise to dyspnea and substernal distress. She had diphtheria in childhood. It has been demonstrated that residual heart block from diphtheria occurs in only very rare individuals.[13] Barring such an assumption, the most likely cause of block at this age would be a congenital lesion, either of the septum or of the conduction fibers themselves. The heart murmur in this patient was not typically that of a ventricular septal defect either in location or intensity. No other congenital lesion was suggested. A tentative diagnosis of a ventricular septal defect with an atypical murmur was made, but such is doubtless an improbable assumption because of the absolute rarity of this condition.

In previously quoted cases[6, 7] with a similar sequence of arrythmias, quinidine was quite ineffectual in therapy, as it proved to be in this instance. The use of atropine in similar cases has been suggested to be of value.[14, 15] Lately procaine intravenously has been advocated in ventricular tachycardia and fibrillation, both for prophylaxis and for emergency use on the operating table.[16] Should another case similar to the one here reported be encountered, a trial of Pronestyl (procaine amide hydrochloride) would seem worth while.[17]

SUMMARY

A case history is presented of a woman with heart block of at least 26 years duration, who died at the age of 47 with Adams-Stokes attacks precipitated by paroxysms of ventricular flutter followed by ventricular tachycardia, ventricular standstill and complete auriculoventricular dissociation. At postmortem exami-

nation the only significant abnormality was the presence of a large aneurysmal defect of the ventricular septum.

ACKNOWLEDGMENT

We are indebted to Dr. Ernest MacDougall of Wilmington, Massachusetts, who referred this patient to us.

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Arterial Hypertension in Dogs

I. Methods

By HENRY A. SCHROEDER, M.D., AND MELVIN L. GOLDMAN, M.D.

Various methods were devised in attempts to produce chronic hypertension in dogs. The induction of anxiety was unsuccessful. Bilateral renal denervation combined with injections of epinephrine appeared to produce temporary hypertension. Permanent hypertension was induced by unilateral renal ischemia with the other kidney left intact only in dogs of nervous temperament. Certain dogs were extremely resistant to the development of hypertension even when several methods were combined. Neurogenic hypertension induced by section of the moderator nerves is probably a true hypertension. It is obvious that the host factor may be as important as the method employed.

METHODS for producing chronic arterial hypertension in laboratory animals have been widely used since the discovery of Goldblatt that partial constriction of the renal arteries was effective.[1] Chronic "renal" hypertension has been initiated in thousands of laboratory animals during the past 15 years, many accessory influences evaluated, and much discussion promulgated concerning the similarities and dissimilarities of the laboratory disease with human arterial hypertension.[2] From a review of the existing work, however, it would appear that the methods used have become so standardized that important questions, especially certain ones relative to the human variety, have been left unstudied. Since much of the purpose of producing laboratory hypertension is for comparative analysis, other factors believed to contribute to and result from the human variety have deserved investigation.

Some of the considerations which arise in any comparison of animal and human hypertension are as follows: (1) the hereditary trait, (2) the psychogenic influence, (3) neurogenic influences, and (4) the effects of hypertension upon other organs, notably the kidneys. Studies involving rats and rabbits have attempted to evaluate certain of these factors, but the general tendency among physiologists to use the dog as a laboratory animal has prevented wide acceptance of many valid conclusions, inasmuch as this animal often will not react similarly to the same procedures. One is forced to the conclusion that the rat and the rabbit are themselves prone to develop hypertension, while the laboratory dog may be singularly resistant. Because many experiments which might apply to human beings cannot be reproduced in the dog, unjustifiable criticisms have been leveled at excellent researches in comparative physiopathology.

For many years we have suspected that certain dogs are susceptible to hypertension while others are resistant.[3, 4] Similarly certain human beings appear to be susceptible, while others are resistant.[5] A breakdown and study of several known factors contributing to hypertension might be rewarding in the assessment of resistance or susceptibility. Therefore, the present program was begun five years ago. Some of the results contribute only negative evidence, many are equivocal, but certain ones deserve reporting.

The study was divided into five parts, of which four are herewith presented: First, normal standards for the population were established. The second portion dealt with attempts to produce arterial hypertension in dogs by psychic stimuli and was unsuccessful. The third attempted to evaluate neurogenic influences and chemical effector substances. The fourth was concerned with hereditary and other factors as accessories to the production of renal hypertension. The fifth, which will be

From the Hypertension Division, Department of Internal Medicine, and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Mo., under a grant-in-aid from the National Heart Institute, United States Public Health Service.

reported subsequently, involved the effects of long sustained chronic hypertension upon the development of arteriolar nephrosclerosis. A controversy exists at present as to whether arteriolar sclerosis is the result of, or precedes, the hypertension[6, 7]; this portion of the study answers that question in the case of the dog.[8]

Methods

All dogs, except when specifically designated, were obtained from the St. Louis City Pound and represented the great variety of cross-breeding usually found in pound dogs, with an intermingling of purer breeds. They were housed in individual cages in a dimly lighted animal room, were cleaned and exercised in a run daily and were fed a diet of Purina Checkers and horsemeat. They were dipped in an insecticidal solution monthly. Measurements of "mean" blood pressure were made in a quiet, light room by the same individuals. The animals lay on a metal table with one hind leg secured; they soon became completely accustomed to the procedure. A mercury manometer with a needle inserted into the femoral artery without local anesthesia was employed. When systolic and diastolic pressures were obtained, a dark, red-lit laboratory with a similar table was the environment. Measurements were made at intervals varying from daily to twice a week, depending upon the requirements of the experiment. Operations were performed under anesthesia with pentobarbital, using aseptic technic. Renal ischemia was induced by a Goldblatt adjustable silver clamp placed about the renal artery and tightened to a point at which approximately 75 per cent of the lumen of the vessel was occluded. Perinephritis was induced by enclosing the kidney in a bag of silk according to the method of Page,[9] care being exercised to avoid constriction of the pedicle. Postganglionic renal denervation was performed by carefully stripping artery, vein and ureter of all visible nerves and plexi with a probe, and by painting the areas with 5 per cent phenol washed off with 70 per cent ethyl alcohol after one minute. "Neurogenic" hypertension was induced in two stages by removal of the left vagus nerve in the neck and careful stripping of both carotid sinuses including the adjacent arteries, followed by the application of phenol; removal of the medial third or two-fifths of the right vagus nerve was accomplished several days later. This procedure effectively removes the "moderator" nerves. Complete postmortem examination was performed in all animals but those still living, in order to confirm the pathologic changes caused by these procedures.

In the following discussion, "slight" hypertension refers to an elevation of average mean blood pressure of 15 to 30 mm. Hg, "moderate" hypertension to an elevation of 30 to 60 mm. Hg, and "marked," to an elevation of more than 60 mm. "Transient" hypertension is considered to be one in which the elevation of blood pressure lasts for three months or less, regressing completely to control values, while "permanent" refers to one existing as long as the dog remains alive without signs of regression.

Results

I. *Normal Standards*

The initial mean arterial blood pressure of 100 dogs from the city pound varied from 91 to 198 mm. Hg with a mean of 137.5 mm. The distribution curve suggested the possibility of a mixture of three types of population, that with a low blood pressure, that with a "normal" blood pressure, and that with a "high" blood pressure. When the third pressure (measured 10 days later) was compared, a similar type of curve was evident (fig. 1).

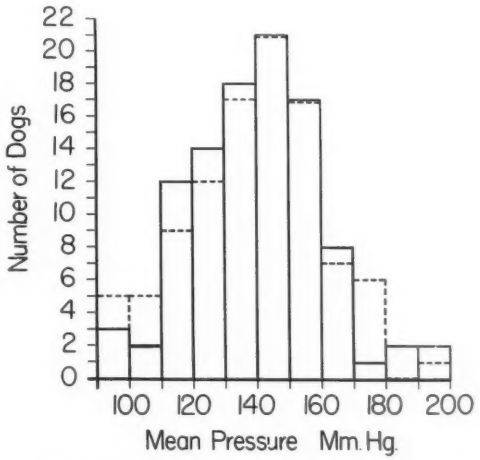

Fig. 1. Distribution of mean arterial pressure in 100 dogs. The solid lines indicate the initial pressure; the dotted lines indicate the third pressure made 10 days later. There is a wide distribution with a few more animals with low and high pressures than would be expected.

The occurrence of "spontaneous" hypertension in mongrel dogs cannot be excluded by any study such as this. Therefore, a comparison was made between the trends of blood pressure of dogs arbitrarily divided into two groups. Ten representative animals were selected which had initial levels of 150 mm. Hg or less, and their first 10 readings, obtained twice a week,

analyzed (fig. 2). The mean for the initial reading was 129.7, that for the fifth 122.1, for the tenth 129.9 mm. Hg. The fifteenth and twentieth readings were 138.9 and 130.3 mm. Hg. While no significant differences appeared, the mean for the third reading was the lowest, 113.6. Therefore it would appear that "training," up to 10 or even 20 repetitions of the same procedure, did not affect the level of blood pressure of animals falling into this range.

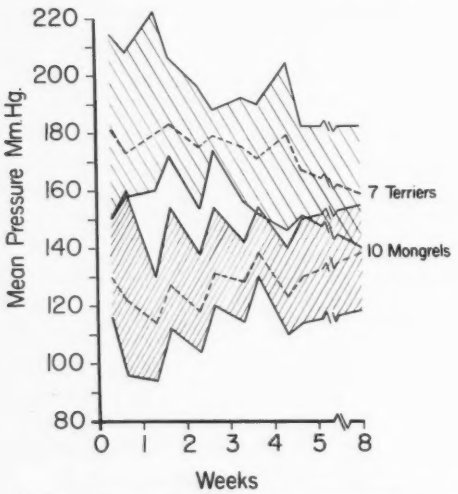

FIG. 2. Chart of mean arterial pressure of 10 mongrel dogs having initial levels of 150 mm. Hg or below, and of seven terriers. The hatched areas indicate the extremes of pressure for the two groups; the broken lines the means. Note that there is a tendency for the mean pressure of the mongrels to rise and that of the terriers to fall during eight weeks of observation.

As a counterpart, the levels of 10 dogs with initial readings of 151 to 160 mm. Hg, five with readings of 161 to 170, and three with readings of 187 to 196 were similarly treated. The initial mean pressure of the first group was 156.4 and the tenth 153.7, indicating no significant decline; of the second group 165.2 and 159.3, showing a slight decline, and of the third 191.2 and 187.3 mm. Hg, suggesting maintenance of elevated blood pressure in spite of "training" of this length of time. An examination of the type of dogs in these three groups revealed that all of the last and five of the remaining 15 were considered to be of the "terrier" type. A further grouping was made on an arbitrary basis; all dogs with five or more out of 10 pressure readings of 160 or more were analyzed separately (eight animals). The initial reading was 171.8, the tenth 166.8, and the fifteenth 158.4, showing a moderate decline. Further falls were seen in the twentieth and twenty-fifth readings of two of these animals, but not to "normal" levels. All but one were terriers. These results suggested that certain types of dogs might be susceptible to hypertension. Exclusion of these dogs from this group of 18 readjusted the final mean pressure of the remainder to 144.3, a decided fall from the initial level. "Spontaneous" but reversible hypertension therefore appeared to be present in 8 per cent of animals by the above definition, and by a less rigorous one the figure would be much larger.* Six purebred but unregistered wire-haired fox terriers, litter mates, were purchased from a pet shop, and one procured from the pound. All showed high initial levels of pressure of 160 to 196 mm. Hg which subsided only slowly. Figure 2 shows a comparison of the findings in this group with those of a comparable group of mongrel dogs. Random increases of pressure to 160 mm. Hg or more on single occasions continued to appear as long as the animals were followed (several months).

II. *Effect of Psychic Stimuli*

An attempt was made to ascertain whether or not induced anxiety or neurosis in normal dogs would lead to elevation of blood pressure. In addition, the effect of anxiety upon dogs which had had transient renal hypertension and recovered was studied, such animals being considered as "potentially hypertensive."

* The average systolic blood pressure of 50 "normal" pound dogs obtained in New York was 174, the average diastolic 102 mm. Hg; the ranges of variation were so great as to make statistical analyses meaningless.[10] Hamilton manometric tracings were used for these figures. Obviously dogs obtained from these two sources, St. Louis and New York, were similar insofar as variations were concerned. Ranges of anesthetized dogs were also very wide; while the usual level of diastolic pressure was 80 to 110 mm. Hg, values as high as 150 to 160 have been seen not infrequently.

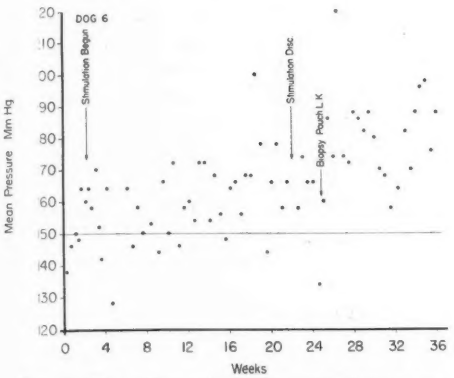

FIG. 3. The effect of psychic stimulation on a terrier. Each dot represents a single determination of mean blood pressure. The stimulation in this case consisted of hanging the dog comfortably in a sling and ringing a bell at repeated intervals two hours a day. The horizontal line at 150 represents the highest control pressure but one. Note that there appear wide fluctuations upward as the procedure was continued. Further elevation of blood pressure occurred following the application of a silk pouch to the left kidney and the taking of a biopsy. The experiment was performed during the fall and winter months.

Six dogs were chosen to be subjected to a form of irritating stimulus at repeated intervals in the hopes that temperamental changes might be induced. The experiments were of a preliminary nature and were inconclusive; they involved subjecting animals to galvanic shocks of 10 seconds' duration every eight minutes for two hours a day, each shock being preceded by the ringing of a bell. The animals were suspended comfortably in a sling during the experiment. The shocks were mild.

Of two control animals subjected daily to suspension in the sling and the repeated ringing of the bell for four months, one, a terrier, appeared to develop instability of blood pressure, his average rising from 150 mm. Hg or below to approximately 165 mm. and remaining elevated for a month after the procedure was discontinued (fig. 3). Wide variations to lower levels were observed. Subsequently the application of a silk pouch about one kidney caused a further elevation of blood pressure for three months, when the dog died

TABLE 1.—*Effect of Renal Denervation on Production of Hypertension in Dogs*
(Mean Arterial Pressure in mm. Hg)

Dog No.	Control Period			Postoperative Period			Duration of Response *Days*	Average Increase	Remarks
	Highest but One	Lowest	Average	Highest but One	Lowest	Average			
				Renal Denervation					
9	140	100	126	182	126	151	225	25	Died of subsequent operation
25	134	102	118	154	132	144	30	26	Epinephrine given subsequently
				Renal Denervation and Perinephritis					
26	148	110	138	144	96	122	—	−16	Epinephrine given previously
28	146	104	131	184	152	167	30	36	Died of heat
30	140	104	121	146	130	142	14	21	Died of infection
36	136	114	125	148	130	138	30	13	Epinephrine given subsequently
11	162	110	147	156	140	150	12	3	Epinephrine given subsequently
				Perinephritis					
22*	142	96	128	162	92	143	70	15	Typical expected response
7*	138	118	132	160	130	144	30	12	Typical expected response

* This type of response was seen in nine animals. Illustrative examples only are given as references to other procedures.

as a result of hot weather. No rise in blood pressure was observed in the other. The addition of the galvanic shock to a third normal dog had no effect on the level of blood pressure, although the animal became irritable and excitable.

Two dogs were operated upon and Goldblatt clamps applied to their left kidneys. Transient hypertension occurred. A month later they

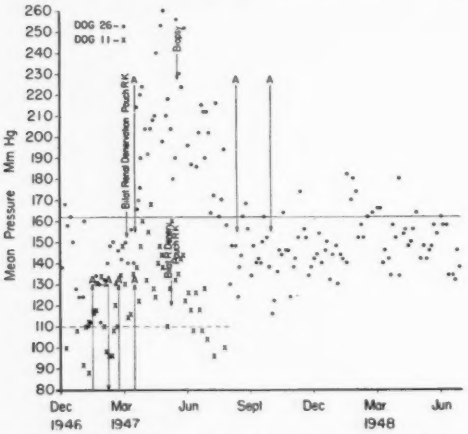

FIG. 4. The effect of the injection of epinephrine upon blood pressure of two dogs. The upper series of dots indicates the response to an injection of 1.0 mg. in oil (arrow A) following the application of a silk pouch to the right kidney and bilateral renal denervation. Note the rather high levels of mean pressure which resulted. The horizontal line represents the highest control pressure but one. Subsequent injections caused very little change. The lower series of crosses show the mean pressure levels of a normal dog. Note the rather prolonged elevation of blood pressure following repeated injections of epinephrine. The subsequent application of a silk pouch and bilateral renal denervation did not cause further elevation of blood pressure. The hatched horizontal line indicates the highest control pressure but one.

were subjected daily to both bell and shock for five months. Their hypertension regressed as would have been expected had no stimuli been given. In a third dog silk perinephritis was induced in one kidney and two months later the animal was exposed in a specially constructed cage to repeated bell-ringing and shocks every 15 minutes around the clock for two months. No hypertension resulted in spite of the development of nervousness and irritability.

It appeared, therefore, from these few experiments, that repeated irritating stimuli given to dogs did not affect the course of hypertension; a minimal stimulus (bell) given to one terrier resulted in a definite but small elevation of blood pressure. The detectable difference between the positive and negative results lay in the natures of the dogs; all but one were mongrels resembling, at the most, hounds.

III. *The Effect of Neurogenic and Hormonal Factors*

This portion of the study was divided into three parts; first, the effect of injections of epinephrine; second, the influence of renal denervation and presumably sensitization of the renal vascular bed to circulating vasoconstrictor substances; and third, evaluation of the results of section of the moderator nerves. Various combinations of these procedures were employed, including the addition of unilateral perinephritis to them. If increased sensitivity of the renal vascular bed to epinephrine results from renal denervation,[10, 11] it was believed that the consequent vasoconstriction might cause increased production of renal pressor substances and initiate a "vicious circle" leading to sustained or at least transient hypertension after the epinephrine had been destroyed.

Denervation of both kidneys was performed in seven dogs. In one slight elevation of blood pressure occurred for a month; in another it lasted over seven months (table 1). Perinephritis due to silk was also induced in one kidney of each of the remaining five animals. Transient hypertension developed in only two. Perinephritis alone was induced in one, section of the moderator nerves in one, and both procedures in one animal each.

A. *Effect of Epinephrine.* Single injections of 0.5 to 1.0 mg. of epinephrine in oil did not materially affect the level of blood pressure of normotensive dogs when readings were made 24 hours later. In two animals, however, slight elevations occurred when injections were continued for 7 to 16 days, lasting over a month (fig. 4). The material, however, induced edema, infection and even severe sloughing of

tissues on repeated administration; therefore, epinephrine solution (1.0 mg. per milliliter) was also employed in doses of 0.5 mg. twice a day for two weeks.

One dog with kidneys denervated 10 days previously developed slight hypertension for two months after injections of epinephrine daily for 18 days. Two others with perinephritis and denervated kidneys developed slight and severe hypertension (table 1). was combined with silk wrapping of one kidney, hypertension of even transient nature did not develop in two of five dogs; in two it was of slight, and in one of moderate degree. Normally, elevation of blood pressure for several weeks or months follows this procedure. The two failures are unexplained. Apparently the denervation acted in some way to minimize the hypertension expected by each of these procedures (table 2).

TABLE 2.—*Effect of Epinephrine on Blood Pressure of Dogs*
(Mean Arterial Pressure in mm. Hg)

Dog No.	Control Period			Treatment Period			Duration of Response *Days*	Average Incr.	No. of Injections	Remarks
	Highest but One	Lowest	Average	Highest but One	Lowest	Average				
Controls										
26	110	88	102	160	114	141	40	39	16	In oil
31	136	98	124	156	130	147	44	23	7	Intraperitoneal in oil
Renal Denervation										
25	134	102	119	172	110	144	60	25	18	In saline
Renal Denervation and Perinephritis										
36	148	130	138	166	140	148	15	10	16	In saline
11	162	110	147	256	162	210	100	63	1	Subsequent single injections gave little response
Perinephritis										
20	150	120	142	158	120	138	—	−4	3	In oil
Moderator Nerve Section										
21	256	176	217	230	166	198	—	−19	3	In oil
Moderator Nerve Section and Perinephritis										
12	172	120	151	160	112	145	—	−6	4	In oil

In one dog, hypertension lasting four and one-half months occurred after a single injection of 0.5 mg. in oil given 11 days after operation (fig. 4). Epinephrine was of only slight temporary effect in one dog which had recovered from hypertension induced by unilateral perinephritis, in one subjected to section of the moderator nerves, and in one subjected to both procedures.

B. *Effect of Renal Denervation and Unilateral Perinephritis.* When bilateral renal denervation

C. *Effect of Renal Denervation and Section of the Moderator Nerves.* "Neurogenic" hypertension did not result from section of the moderator nerves in two dogs previously subjected to bilateral renal denervation. Neither exhibited even transient elevations of blood pressure. In one the section was extensive enough to cause death two weeks after operation.

D. *Effect of Section of the Moderator Nerves.* Twenty dogs were subjected to extirpation of

the carotid sinus and aortic depressor nerves. The purpose of the experiment was to determine whether or not this form of "neurogenic" hypertension was a true chronic diastolic hypertension, or was merely secondary to increased cardiac output or transitory nervous

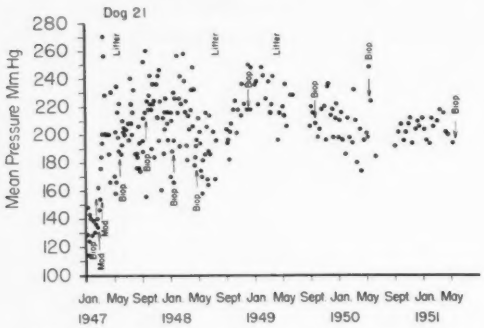

FIG. 5. Hypertension induced by section of the moderator nerves. "Mod." refers to section of the nerves, and "Biop." to a small renal biopsy of the right kidney. At "Litter" the dog delivered seven, six and six living puppies respectively. Note the sustained elevation at a level of 200 mm. Hg or more lasting over four years.

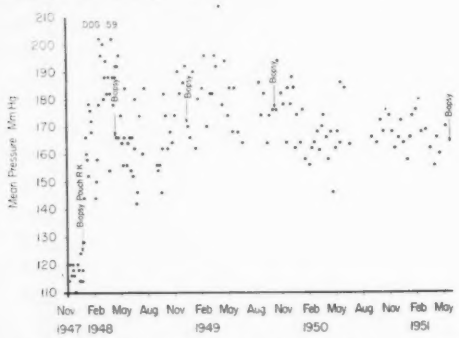

FIG. 6. Moderate hypertension induced by the induction of unilateral perinephritis. Only the right kidney was wrapped in silk. Note the sustained elevation for three and one-half years. Biopsies were obtained from the left kidney. This chart is typical of others of dogs similarly treated (See text).

vasoconstriction. Goldblatt has expressed the latter opinion, believing that the "basal" blood pressures of such animals are normal.[12]

Three of these animals have shown a sustained severe hypertension for four years, with levels which are usually above 200 mm. Hg. One has delivered three litters of puppies without demonstrable change (fig. 6). Nine were used for various purposes in brief experiments after hypertension had become unequivocably established; under anesthesia induced by Pentothal sodium or pentobarbital, blood pressures remained markedly elevated, and diastolic pressures obtained with a Hamilton optical manometer were very high. Except by specific treatment with certain drugs it was found impossible to lower the blood pressures of these dogs to normal levels; during rest, sedation, anesthesia, quiet or other simple measures they remained high. Our experience was similar to that of others.[13] Furthermore, vasoconstriction was demonstrated in local vascular beds, especially the mesenteric, which was of marked degree.[11] Diastolic pressure levels under anesthesia varied from 130 to 230 mm. Hg. Failure to produce chronic hypertension occurred in six, and the procedure was only slightly successful in two dogs.

IV. *The Effect of Renal Factors*

The production of chronic hypertension by bilateral constriction of the renal arteries or by unilateral constriction and contralateral nephrectomy is so well known as to deserve little comment. The occasional failures are worthy of note, however, when no ready explanation for them is offered.

The larger portion of this study was concerned with the production of chronic arterial hypertension by unilateral renal arterial constriction or unilateral perinephritis induced by silk *without* contralateral nephrectomy. Previous experience had demonstrated that some dogs were susceptible to this procedure and others resistant.[10] Therefore 33 dogs were operated upon, Goldblatt clamps being applied in the cases of 21 and silk pouches in 12. The expected sequence of events was a slight or moderate hypertension lasting one to three months[2]; this was found in only nine. Chronic sustained hypertension, however, was induced in 15. Ten are living at the time of writing, five having exhibited moderate to marked hypertension for four to four and one-half years, and five for one to three years.* Three of

* The mean arterial pressures of these dogs in March 1952 were 170, 178, 186, 186, 190, 192, 204, 216, 216, 228 mm. Hg. Hypertension has therefore been sustained for two to more than five years.

these dogs were litter mates of a neurogenic hypertensive mother and were seven months old at operation; all had blood pressures in the low "normal" range during the control period of three months (125 mm. Hg or below). In seven others the control levels fluctuated to that either differences in technic or differences in the fundamental nature of the animals was responsible. Therefore attempts were made to induce "neurogenic" hypertension superimposed upon renal ischemia, by extirpation of the aortic depressor and carotid sinus nerves.

TABLE 3.—*Sustained Hypertension Resulting from Unilateral Renal Affections*

	No. Dogs	Slight Elevation B.P.	Mod. Elevation B.P.	Marked Elevation B.P.	Tempo-rary	Perma-nent	Complete Failures	Duration of Hypertension (weeks)	Remarks
Silk Perinephritis									
	12						2		
		1			1			1	
			3		2	1		>8–18	
				6		6		>200	One died at operation 6 mos. later
Goldblatt Clamp									
	21						7		
		3			3			4–8	
			9		3	6		12–36	4 used in experiments, 3–6 mos.
				2		2		>13–20	
Goldblatt Clamp and Moderator Nerve Section									
	2	1	1		2			4	
Silk Perinephritis and Moderator Nerve Section									
	7						4		
			1			1		40	Died at operation
				2		2		>225	
Total.....	42	5	14	10	11	17	13		
Permanent Hypertension: 20 (More than 4 years, 10) Temporary Hypertension: 9									
Controls—Bilateral Renal Affections or Unilateral with Contralateral Nephrectomy									
	17	5			5		0	4–65	One apparently permanent
			9			9		8–52	
				3		3		8–90	
Total.....	17	5	9	3	5	12	0		

150 mm. Hg, and in one to 170. Four terriers exhibited persistent hypertension for many weeks during the control period, fluctuating toward "normal" only late. On the other hand, the procedure failed to elevate blood pressure even temporarily in nine.

These distinctly divergent results suggested In 5 of 10 dogs a combination of both procedures failed. In two, severe hypertension lasting four years resulted, and in three, only extirpation of the moderator nerves was successful, the silk pouch causing either no or but slight hypertension. In two, slight transient elevation of blood pressure followed each

operation. In susceptible animals, unsuccessful section of the moderator nerves causes a severe but transient hypertension of several weeks duration. It is unlikely that errors in technic were responsible for these results, for our method has erred on the side of too extensive section rather than too little, often causing death from avagotonia a few days after operation. It is therefore possible that differences in susceptibility to "neurogenic" hypertension also exists in dogs.

A similar, but less frequent, finding was the failure of severe hypertension to develop when all of the renal tissue was ischemic. Constriction of both renal arteries, constriction or the induction of perinephritis in one kidney with contralateral nephrectomy, and the induction of bilateral perinephritis either by silk or by covering the kidneys by rubber finger cots was performed in 17 dogs. Failures occurred in five, only a slight transient hypertension resulting (table 3). Attempts to produce hypertension by tightening the clamps were of no avail. Since this procedure is well known to be successful in a large majority of dogs, the failures cannot be ascribed to errors in technic, but must have been due to some inherent quality in the animals themselves.

Successful production of chronic hypertension in 15 dogs by unilateral renal ischemia alone was of special interest to the problem. In two, the kidney affected by silk extruded from the skin several months after operation and was either removed or sloughed off. The hypertension was unaffected. Nephrectomy was not performed in the others. Repeated biopsies of the opposite kidney at 6- to 12-month intervals have been made in order to observe the appearance and progression of vascular changes; the results will be reported subsequently, but leave little doubt that renal vascular disease is a result, and not a cause, of chronic hypertension.[8]*

Discussion

From the experience reported here, it appears that individual dogs exhibit marked differences in susceptibility or resistance to the development of chronic hypertension induced by various means. The range varies from almost complete immunity to several of the procedures employed, to an extreme susceptibility to one of them. Furthermore, in certain types of dogs, especially those of the terrier breed, hypertension is easily induced (table 4). These findings are not surprising when one considers the variations in temperament from dog to dog and breed to breed. Obviously a study of the incidence of "spontaneous" hypertension or susceptibility to experimental hypertension in pure breeds of dogs would be rewarding.

Failure to produce experimental hypertension in certain animals by a combination of the known successful procedures is as important to any study as is success. The essence of immunity may concern pathogenesis intimately. The present experience leaves unanswered questions of this nature, at the most merely pointing out the wide variations found.

There appear to be no "normal" levels of blood pressure of pound dogs. The distribution curve shown in figure 1 is typical, except for the extremes, of a large spread of values in a population. Since we are dealing with a condition, hypertension, which may or may not be present in the normal population and may or may not be prevalent, it is difficult, if not impossible, to state with accuracy wherein lie the upper limits of "normal." We have used a rough rule of thumb in considering 140 mm. Hg as the upper limit of "normal" mean pressure, but our findings do not justify this assumption for more than a majority of animals subjected to training. Until larger populations have been studied, we cannot draw the line between "normal" and "high" blood pressure for the dog, as we do so confidently for man. It is certain that dogs as a rule exhibit much higher arterial pressures than do rats or human beings; only about 9 per cent of the present series were in the range of normal values.

* The first demonstrable changes were in the basement membrane of the glomerular capsule, characterized by thickening. These appeared in 6 to 12 months and have been slowly progressive. Thickening of the tuft was usually seen; the arteriolar changes at the present stage are slight but definite.

An evaluation of the results of this study suggests that, in spite of apparent changes in the temperaments of the dogs, subjecting them to irritating stimuli failed to change the level of blood pressure. From this small series it would appear that the type of animal was a more important factor than the stimulus. Although the dogs became chronically nervous, and excitable, the only one to show a significant elevation of blood pressure was a control terrier not subjected to the shocks. Experiments designed to impose psychic factors upon renal ischemia failed completely to induce hypertension in mongrel dogs.

Chronic hypertension was easily induced in certain dogs chosen for the purpose by reason of (a) high initial blood pressure, (b) excitable temperament, (c) terrier, collie or spaniel breed, and (d) an over-all impression of behavior under handling. The first of these requisites was not always necessary. In dogs of this type, experimental unilateral renal affections apparently caused chronic hypertension readily (in 45 per cent). On the contrary, certain other animals not responding even temporarily to this procedure were resistant to bilateral affections (in 29 per cent). Therefore, the differences in response can be explained in two ways, by errors in technic or by differences in the host. We do not subscribe to the former explanation; perinephritis induced by silk was equally as extensive in the hypertensive as in the normotensive animals, and pathologic changes in the kidney affected by a Goldblatt clamp were also similar. Furthermore, these experiments were designed to produce hypertension in as many dogs as possible.

TABLE 4.—*Summary of Results of Various Procedures to Induce Chronic Arterial Hypertension in Dogs*

Procedure	Total No. Dogs	No. Dogs in Exp.	Failed	Slightly Successful	Successful	% Successful
Psychic Stimuli	6					
Control		3	2	1		0
Unilateral Renal Ischemia		3	3			0
Neurogenic Influences	47					
Epinephrine		2		2		0
Renal Denervation		2			2	100
Same + Unilateral Perinephritis		5	2	3		0
Epinephrine Added to Above		3		1	2	67
Unilateral Perinephritis & Moderator Nerve Section + Epinephrine		3	3			0
Moderator Nerve Section		20	6	2	12	60
Moderator Nerve Section and Renal Denervation		2	2			0
Same + Unilateral Perinephritis		10	3	2	5	50
Renal Influences	50					
Unilateral Perinephritis		12	2	3	7	58
Unilateral Renal Ischemia		21	7	6	8	38
Bilateral Renal Ischemia or Perinephritis		17	5		12	71
		103	35	20	48	47

Type of Dog (Unilateral Renal Affection Only)			
Terrier	0	4	
Collie	2	4	
Spaniel	1	1	
"Mongrel"	10	5	
Assorted Breeds	5	1	
	18	15	

Indeed, animals appeared resistant to the induction of "neurogenic" hypertension as well as "renal" hypertension (in 40 per cent). Variations in technic might account for these differences, had not repeated attempts to remove the moderator nerves been made in several. Resistance to other procedures cannot be conclusively demonstrated in such small series, but the same tendencies appear. Therefore, the conclusion must be drawn that the factor of the host is a most important one in the production of experimental hypertension. Dogs, within their limits, differ in their personalities as much as do human beings; in their breeds and physical structures much more so; it is entirely possible that their individual reactions to a single pathologic alteration may show great variability. This factor is of obvious importance in any study of pathogenesis.

The smallness of the series subjected to various neurogenic influences allows no definitive conclusions to be drawn. There are, however, suggestive trends which bear further confirmation. Renal denervation was apparently followed by moderate hypertension, but when combined with the production of unilateral perinephritis it was much less or not effective. The addition of repeated injections of epinephrine seemed to cause a return of the hypertensive response, whether perinephritis was present or not. Epinephrine did not affect the average level of blood pressure of hypertensive dogs when the kidneys were not denervated; in normotensive dogs there was, however, a sustained but temporary effect. General theories to explain these few findings are lacking.

The ability to produce chronic arterial hypertension in dogs by leaving one kidney intact has provided the opportunity to study pathologic changes in the glomeruli and arterioles of this kidney by means of serial biopsies. The operations leave small scars in the cortex which are often difficult to find a year or two later. Five dogs exhibit chronic hypertension due to unilateral perinephritis, three to section of the moderator nerves, and two to a combination of both. Fifteen others have died at intervals of six months to three years, and there are large numbers of controls. Pathologic lesions have not developed until the hypertension has lasted two years or more.

Summary and Conclusions

1. Various influences, psychic, neurogenic, renal and hereditary, were assessed in attempts to produce chronic experimental hypertension in 103 dogs.

2. Dogs exhibited various degrees of resistance and susceptibility to experimental hypertension.

3. Chronic arterial hypertension has resulted from unilateral renal affections when the contralateral kidney was left intact. The type of dog susceptible to this procedure can be fairly readily predicted.

4. Certain dogs failed to develop hypertension even when both kidneys were affected, when the moderator nerves were sectioned, or when both influences (neurogenic and renal) were superimposed.

5. Renal denervation appeared to increase the susceptibility of dogs to hypertension, especially when epinephrine was injected daily.

6. Repeated irritating stimuli accompanied by changes in personality failed to cause hypertension even when unilateral renal ischemia was induced.

7. The "host factor" in experimental hypertension deserves further study.

Acknowledgments

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The Effect on Blood Pressure in the Right Heart, Pulmonary Artery and Systemic Artery of Cardiac Standstill Produced by Carotid Sinus Stimulation

By CHARLES V. DOWLING, M.D., WARREN W. SMITH, M.D., ADOLPH R. BERGER, M.D., AND ROY E. ALBERT

In two patients with hypersensitive carotid sinus syndrome, cardiac standstill was induced while pressures were recorded in the pulmonary and femoral arteries and right heart. With onset of ventricular standstill, pressures in the right atrium and right ventricle equalized and gradually increased, that in the femoral artery decreased, and that in the pulmonary artery fell until it became equal to right ventricular pressure, and then increased commensurately with it. All pressures then approached a uniform magnitude asymptotically: this uniform pressure is believed to correspond to the "static pressure." The manner in which the respective pressures returned to normal with resumption of normal cardiac rhythm is described, and certain unexpected findings are discussed.

ALTHOUGH the syndrome of carotid sinus sensitivity has been the object of considerable study,[1–3] measurements of intracardiac and pulmonary arterial pressures during cardiac standstill in living man have not been reported. This presentation is the description of the measurements of these pressures during ventricular asystole induced in two patients by the stimulation of a hypersensitive carotid sinus in each.

PROCEDURES AND METHODS

The patients were white men 44 and 67 years of age respectively. The former (G. S.) had been admitted to the hospital because of recurrent syncopal episodes which were considered to be due to hypersensitive carotid sinus syndrome. In the latter (K. H.), carotid sinus hypersensitivity was an incidental finding. This patient had diabetes mellitus, and moderate elevation of the systolic blood pressure, probably due to arteriosclerosis.

Cardiac catheterization was done with a double lumen catheter; pressures from the catheter lumens and from an indwelling brachial or femoral arterial needle were recorded by Hamilton manometers simultaneously with respiratory movements of the chest wall, recorded by means of a pneumograph, and one lead of the electrocardiogram. All measurements were made with the patient in the postabsorptive state and lying supine. The right carotid sinus was stimulated by externally applied digital pressure. The tracings presented in this report illustrate changes following stimulation of the right carotid sinus. In each patient asystole was induced during the simultaneous recording of pulmonary arterial and right ventricular pressures, and again while recording simultaneously right ventricular and right atrial pressures.

RESULTS

The pressures in the right heart and pulmonary artery of each patient were normal during the control periods. In both patients ventricular asystole promptly followed stimulation of the carotid sinus, and lasted from 5 to 10 seconds, terminating in resumption of ventricular contractions despite continued pressure on the sinus.

In each instance, ventricular asystole occurred abruptly without any preliminary alteration of rhythmic cardiac contractions. With the onset of ventricular stand-till, peripheral arterial pressures immediately diminished (fig. 1), rapidly at first and then more

From the Department of Medicine, New York University College of Medicine, and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

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slowly, falling to lowest values ranging from 14 to 22 mm. Hg. The right atrial and right ventricular pressures concurrently tended to equalize, and increased through an average of 6 mm. Hg. Pulmonary artery pressure at first fell until it was slightly less than right ventricular pressure, after which pulmonary artery and right ventricular pressures increased commensurately.

One or two atrial contractions occurred during ventricular standstill in two instances (figs. 1 and 2). The resulting pressure increment within the atrium is reflected by pressure increases of similar magnitude in the right ventricle and pulmonary artery. In certain tracings (fig. 2) there are visible momentary increases of the femoral arterial pressure coincident with atrial systole. Similar pulses were described by Wiggers[4] and have been seen in many other tracings in this laboratory: they probably are caused by transmission of the pressure pulse from the left atrium through the left ventricle to the closed aortic valve.

The various pressures were influenced to a progressively increasing degree by the vigorous respiratory movements of the hyperpnea that developed after five to nine seconds of cardiac arrest. Expiration augmented, and inspiration reduced, all pressures. It is likely that the pneumograph, which merely indicates movements of the chest wall, is not, in point of time, a reliable index of intrathoracic pressure when respirations are abrupt. This deficiency may explain the apparent coincidence in some records (figs. 2 and 3) of a drop in all measured pressures with the attainment of maximal expiration.

With the resumption of ventricular contractions the peripheral arterial systolic and diastolic pressures rose progressively with each beat. In no case was the peripheral arterial pulse pressure greater during recovery than in the control period. In contrast, in certain instances (fig. 2) some of the first cardiac contractions were accompanied by higher systolic, diastolic and pulse pressures in the pulmonary artery than during the control period at comparable phases of respiration. When such increases in pulmonary artery pressure occurred, they apparently developed with those systoles which accompanied the inspiratory phase of respiration.

With resumption of ventricular contractions, the pulmonary artery pressures in every instance returned to control values much more quickly than those in the systemic artery.

Discussion

The course of events following carotid sinus stimulation in these patients may be construed as follows: ventricular arrest occurs with the heart in diastole. The tricuspid and presumably the mitral valves open with diastole as usual, permitting equalization of the atrial and ventricular pressures on each side of the heart. Because the pulmonic and aortic valves are closed, the relatively high pressure in the pulmonary and aortic arteries causes blood to flow into their respective venous beds, distending and increasing the pressure within them. Thus, from the beginning of asystole there is a progressive increase of blood volume and pressure within the systemic venous tree and right heart on one hand, and the pulmonary veins and left heart on the other. The pressure within the pulmonary artery, however, falls for only one or two seconds when it becomes lower than the concurrently increasing right ventricular pressure. At this point the pulmonic valve opens and as pressure in the right heart continues to rise, blood flows into the pulmonary artery causing the pressure within it to rise also. Thus, from the time of opening of the pulmonary valve the combined volume of blood in the pulmonary vessels and left heart increases progressively (with certain interruptions as described below) above that present normally.

From the foregoing analysis, it is clear that during cardiac standstill blood will continue to flow as long as there is a gradient of pressure from the aorta through the greater and lesser circulations to the left ventricle. As asystole continues, this gradient approaches zero and pressures throughout the vascular bed approach a uniform level: static pressure.

The concept of static pressure, suggested by Starling,[5] and studied by Starr,[6, 7] refers to the residual pressure which would exist throughout the entire vascular tree if the

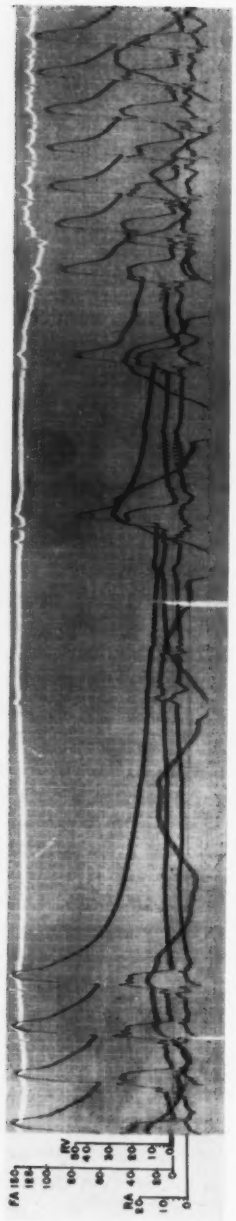

Fig. 1

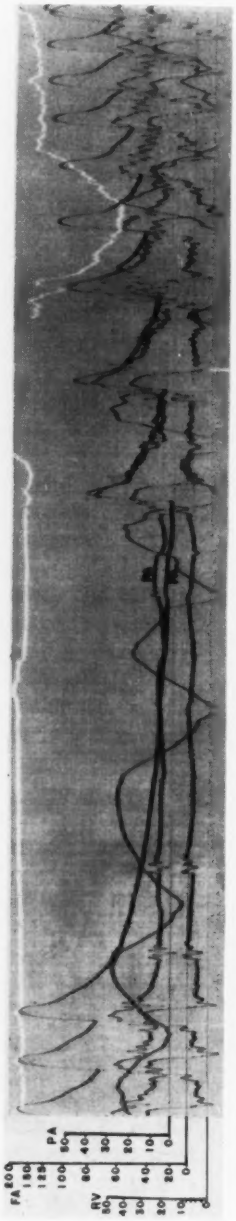

Fig. 2

Fig. 3

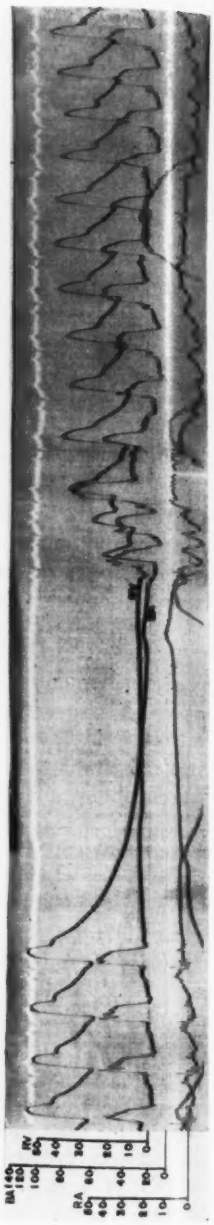

Fig. 4

pumping action of the heart terminated and blood flow ceased. Starr[7] measured intracardiac pressures immediately after death in humans who did not have congestive heart failure, and found static pressure to be 5 to 16 mm. Hg. He recognized that change of vascular tone probably occurs at death, and while his values therefore may be subject to error, they nevertheless were consistent from patient to patient and probably serve as a good index of the actual magnitude of true static pressure.

In the tracings which form the basis for this report, all pressures during ventricular standstill approach a uniform pressure asymptotically. They indicate, therefore, that static pressure in our patients under these circumstances is between 9 and 18 mm. Hg: the upper limit is the average lowest value reached by the peripheral arterial pressure, and the lower limit is the average highest pressure attained in the great veins and right heart. These values are subject to error owing to the influence of the diminution of vascular tonus which may be an element of the response to carotid sinus stimulation in most cases,[3] and owing perhaps to vascular response to asphyxia. Furthermore, it has been shown[8] that respiratory movements can produce circulation of blood through the vascular system in the absence of cardiac contraction. Therefore, even if asystole had been greatly prolonged in these cases, blood flow might never have stopped completely as long as respiratory movements persisted—and static pressure thus would not be reached. However, the nearness of our values to those found by Starr suggest that both approximate the true value for static pressure.

Toward the end of the period of ventricular asystole, all blood pressures were influenced to a greater degree by respirations than during the control period. It is probable that the increased forcefulness of the respiratory movements during cardiac arrest contributes to this alteration. Furthermore, it has been shown above that as asystole continues the volume of blood in the pulmonary vascular bed and left heart becomes greater than in the normal state. As a result the lungs become more turgid than normally and the alterations of thoracic volume due to respiratory movements may be expected to be accompanied by greater pressure variations within the thoracic cavity and the pulmonary vessels.

While it is hazardous to subject records of this type to minute analysis, it nevertheless appears that, of all the pressures, that in the pulmonary artery varies the most with respirations; and that on certain, if not all, occasions the pressure in the pulmonary artery exceeds that in the right ventricle briefly during expiration. Accordingly the pulmonary valve must close momentarily, and the flow of blood from the right ventricle into the pulmonary artery may then be interrupted briefly.

Despite the fact that during cardiac standstill each ventricle probably accumulates a larger volume of blood than in normal diastole, the pulse pressure in the systemic arteries is not increased above control magnitudes in any of the recovery beats. This may be due to two

FIG. 1. Patient K. H. From above downward: femoral artery, right ventricle, right atrium. The pneumogram is superimposed on the intracardiac pressure tracings. In all of the tracings, downward movement of the pneumograph represents inspiration. Ventricular asystole lasted nine seconds. Two atrial contractions occurred during this period. The second of these may have come from an ectopic focus within the atrium, for no typical P is identifiable in the electrocardiogram. Despite the relatively long duration of ventricular asystole, there is no increase in right ventricular pulse pressure during recovery.

FIG. 2. Patient K. H. From above downward: femoral artery, pulmonary artery and superimposed pneumogram, right ventricle. Ventricular standstill lasted 10 seconds. Two atrial contractions occurred during ventricular asystole. Small pulses are identifiable in the femoral artery tracing which coincide with atrial contractions. The pulses in the right ventricle and pulmonary artery are increased in the first, second and third recovery beats.

FIG. 3. Patient G. S. From above downward: brachial artery, pulmonary artery, right ventricle, pneumogram. Ventricular standstill lasted 6.5 seconds. The apparent coincidence of a drop in all pressures with attainment of maximal expiration, during asystole, is probably artefactual.

FIG. 4. Patient G. S. From above downward: brachial artery, right ventricle, right atrium, pneumogram. Ventricular standstill lasted eight seconds. The pulse pressure in the third recovery beat of the right ventricle is greater than in the control.

factors. Peripheral arteriolar relaxation may occur during activation of the hypersensitive carotid sinus reflex.[3] This event in itself would permit an increase in stroke volume to be introduced with relatively small pulse pressure. Furthermore, the process of "run-off" of blood from the arterial to the venous side during ventricular asystole depletes the arterial blood volume and, as a result, the systemic arteries are less distended with blood. This development, too, will permit the introduction of an increased stroke volume with a relatively small increment of pressure.

In every instance the blood pressure in the pulmonary artery returned to normal during recovery much more quickly than that in the systemic artery. In certain instances, the pulmonary artery systolic, diastolic and pulse pressures exceeded those of the control period, whereas this never was the case in the systemic artery. One possible reason for these differences in the behavior of pressure between the greater and lesser circulations is that by the end of asystole the pulmonary vascular bed and left heart contain more blood than normally, while the systemic circulation is correspondingly depleted of blood. Systolic discharges into the somewhat distended pulmonary vessels will, therefore, be attended by relatively higher pressures than in the case of the aortic artery. Further, it is possible that the right ventricle, which is probably more distensible than the left, accumulates a greater presystolic volume than the latter, and its first systolic ejections may be greater than those of the left ventricle. The minor augmentation of blood flow that occurs during inspiration may account for the coincidence of the increase of pulse pressure with this phase of respiration. Why this increase is present in some instances and not in others, despite the coincidence of systole with inspiration, we are unable to explain.

Summary

In two patients ventricular standstill was induced by stimulation of a hypersensitive carotid sinus, while respiratory movements and pressures in the pulmonary artery, right heart, and a peripheral artery were recorded.

In every instance of ventricular asystole, the systemic arterial pressure fell, and right heart pressure rose. The pulmonary artery pressure at first fell until it equalled right ventricular pressure; then it rose commensurately with that in the right ventricle. All pressures then asymptotically approached a uniform magnitude which is thought to approximate "static pressure."

The hyperpnea which developed during asystole exerted an exaggerated effect upon the central blood pressures.

With resumption of ventricular contractions, all pressures returned to the control values. The pressures in the pulmonary artery recovered more quickly than those in the systemic arteries; occasionally the former exceeded the control values during some of the recovery systoles.

Acknowledgment

The authors wish to acknowledge the counsel of Dr. L. W. Eichna, in whose laboratory this work was done.

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Cation Exchange Resin in the Treatment of Congestive Heart Failure

I. Electrolyte Exchanges during Initial Periods of Resin Therapy

By J. R. Elkinton, M.D., R. D. Squires, M.D., and W. C. Klingensmith, Jr., M.D.

Electrolyte balances were measured in four edematous cardiac patients receiving cation exchange resin. It was found that such therapy would increase the fecal loss of sodium and, in some of the cases, would result in the loss of edema which had been refractory to other forms of therapy. In these cases the main route of sodium excretion was through the kidneys and not through the intestinal tract. The resin appeared to potentiate the renal action of simultaneously administered mercurial diuretics.

IN 1946 Dock[1] first suggested the use of cation exchange resins for the removal of sodium from the intestinal tract of patients with edema. Since then a series of investigators[2–9] have demonstrated that such substances will indeed increase the fecal excretion of sodium, and so may be useful in the treatment of edema associated with retention of sodium. On the basis of these studies at least three preparations of cation exchange resin* have been placed on the market by pharmaceutical manufacturers. However, relatively little information as yet is available in the medical literature for the practicing physician, concerning the mode of action, the indications, the contraindications, and the long term results of this therapeutic agent. It is the purpose of these two papers, therefore, to present, in the first, detailed data on the electrolyte exchanges which take place during the initial periods of treatment of edematous cardiacs with resin and, in the second, the clinical results and chemical complications in a large series of patients in whom resin has been an adjunct to therapy over prolonged periods of time.

Theory of Action

Cation exchange resins are extremely stable and insoluble high unit weight polymers. Those used in medicine are usually the phenol-formaldehyde, phenol-methylene or polystyrene types. Their molecular structure resembles that of a crystal lattice due to cross linkages consisting of either phenyl or methyl groups.[10] Attached to this framework are the reactive substituents such as carboxylic or sulfonic groups. The capacity of the resin, or the quantity of ions with which it will exchange, is ultimately determined by the number of cross linkages and the number of reactive substituents per unit weight of resin.[11]

When a resin is placed in a solvent, it tends to swell much the same as does dry gelatin. This facilitates diffusion of the ions to be exchanged throughout the molecular structure of the resin. The reactive substituents behave chemically as if they were a solution of weak acids, the pH of the solvent in which the exchange is taking place determines the extent of their ionization. Therefore, the resin can only

From the Chemical Section and the Edward B. Robinette Foundation of the Department of Medicine, and Hospital of the University of Pennsylvania, Philadelphia, Pa.

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J. R. E. is an Established Investigator of the American Heart Association.

E. D. S. is a Fellow in Medicine assigned to the Chemical Section.

W. C. K., Jr., is a Fellow in Medicine assigned to the Robinette Foundation.

* Resodec, Smith Kline and French Co.; Natrinil, National Drug Co.; Carbo-Resin, Eli Lilly Co.

saturate its capacity at a pH which permits maximal dissociation of the reactive substituents. In addition, the rate of the reaction depends upon the concentration of the reacting ions. Particle size and adequate mixing are likewise important factors in determining the rate of the reactions as they determine the amount of surface area to be exposed for reaction.

Amberlite IRC-50 is a carboxylic resin and behaves chemically as a weak acid. It is said to have an in vitro capacity, under optimal conditions, of 10 mEq. of base per gram of resin. Maximum capacity for this resin obtains at a pH of 10 to 11. The range of variation of pH in the gut is unknown but it probably averages slightly on the alkaline side of a pH of 7. At pH 7 this resin has a capacity of 6.2 mEq. base per gram, rapidly dropping to 3.5 mEq. at pH 6.[12] The time interval required for saturation at this pH is long and therefore the resin perhaps takes up only 2 to 3 mEq. per gram in the few hours it remains in the bowel.[12] Sulfonic resins function as stronger acids and have a more rapid rate of exchange than the carboxylic resins. The optimum pH is 3.

The affinity the resin manifests toward various ions is peculiar to the resin being considered. However, generally speaking, it may be said that cationic exchange resins have a greater affinity for divalent ions, calcium and magnesium, than monovalent ions, sodium and potassium, and the affinity for potassium is greater than that for sodium. Carboxylic resins have a greater affinity for calcium and magnesium than do sulfonic resins.

Little is known about the variations in the total base concentration throughout the gut. Even less is known regarding the individual concentrations of the various cations comprising the total base. It would appear that the concentration of sodium is high enough to more than compensate for the greater affinity of the resin for potassium. The amount of sodium excreted in the feces is often equal to or greater than that of potassium. The amounts of these ions excreted in the stool per unit time are extremely variable. This variability may be accounted for to some extent by incomplete passage of a 24-hour stool. Much remains to be done in order to ascertain what environmental factors within the gut lumen are most favorable to ion exchange. The precise limits of the exchange capacity of a resin in vivo have yet to be determined. Such limits are probably determined by a variety of factors such as the amount of resin ingested, and its rate of movement through the gastrointestinal tract, variations in pH throughout the course of the bowel lumen, and the amount of sodium in the diet and the rate of exchanges of sodium across the intestinal mucosa.

Both cationic and anionic exchange resins are now in use in medicine. Amberlite IRC-50, a carboxylic resin, or one of its modifications, is the most commonly used (single) resin for cation exchange. It has been given to patients in either the hydrogen cycle or the ammonium cycle. The ammonium cycle resin partially converted to the potassium cycle has also been given. The rationale for giving such a preparation is based on the observation that at the pH of the gastric content the resin will be completely converted to the hydrogen cycle. This reaction frees the potassium for absorption into the systemic circulation and thereby helps to compensate for the potassium taken up lower down in the gut.

The ammonium ion released from the resin is absorbed into the enterohepatic circulation and converted to urea by the liver. This reaction produces an acidifying effect similar to that produced by giving ammonium chloride. The base, including sodium, fixed to the insoluble portion of the resin at the higher pH of the small intestine, is excreted in the feces. Thus the amount of sodium absorbed is reduced, tending to produce a negative sodium balance.

Given a negative sodium balance induced by resin, the net effect on the body fluids of the patient will depend in addition upon the associated rates of excretion of water and electrolytes by the kidney. Removal of cation, or base, from the body should result in the renal excretion of water. The tendency to a disturbance in the acid-base equilibrium by the preferential removal of cations, is counterbalanced in the normal kidney by the excretion of a more acid urine containing increased amounts of chloride and ammonia. In patients with lis-

eased kidneys which are unable to produce ammonia, resin administration may lead to relative chloride retention, bicarbonate deficit, and, thus, a metabolic acidosis. Adequate renal function, therefore, is a prerequisite to the successful clinical use of cation exchange resin in edematous patients.

TABLE 1.—*Average Daily Intake and Output, and Total Period Balances of Electrolytes in Four Edematous Cardiacs Treated with Cation Exchange Resin*

Patient	Period	Days	Daily therapy			Weight	Av. daily intake			Average daily output							Total period balance		
										Stool			Urine						
			Resin	Hg	NH_4Cl		Cl	Na	K	Cl	Na	K	Vol	Cl	Na	K	Cl	Na	K
			Gm.	*ml.*	*Gm.*	*Kg.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*ml.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*
G. B.	11/26					74.9													
	11/26–28	2	0			75.0	15	12	198	2	1	32	770	0	1	43	+24	+16	+246
	11/28–12/1	3	25*			75.9	18	15	57	0	3	14	785	0	1	19	+53	+26	+71
	12/1–12/7	6	37*			76.7	18	27	69	—	lost	—	1303	0	2	14	—	—	—
	12/7–10	3	50*			75.7	28	26	81	0	35	50	1205	0	3	6	+81	+55	+75
	12/10–16	6	50*	2		68.9	41	33	175	2	36	45	1544	128	81	28	−547	−528	+538
T. M., I, 1950	4/24					59.2													
	4/24–5/4	10	50*	3	3	55.6	70‡	70‡	?	10	87	45	2858	202	98	53	—	—	—
	5/4–12	8	50*			56.5	70‡	70‡	?	8	68	56	2101	93	17	20	—	—	—
II, 1951	2/6					61.6													
	2/6–8	2	45*			62.7	70‡	70‡	?	2	71	57	910	28	4	63	—	—	—
	2/8–10	2	45*	2		59.7	70‡	70‡	?	10	89	80	3055	362	323	51	—	—	—
L. J.	11/24					67.5													
	11/24–27	3		2		67.3	60	54	95	0	1	7	1860	154	92	81	−284	−115	+22
	11/27–30	3		2	3	68.8	116	57	98	0	2	19	1993	146	73	80	−89	−54	−4
	11/30–12/3	3		2		70.2	60	57	98	1	6	18	1405	51	11	50	+24	+120	+90
	12/3–6	3	45†	2		69.2	46	42	136	0	32	44	1505	54	18	68	−24	−24	+73
J. B.	5/25					—													
	5/25–28	3				64.2	48	7	103	0	3	20	985	6	4	13	+135	±0	+219
	5/28–6/1	4	50†			—	52	7	170	0	13	36	1685	17	1	31	+140	−30	+291
	6/1–9	8	50†	2		62.1	46	7	144	2	21	59	1966	68	12	30	−171	−196	+435

* Ammonium cycle resin.

† Ammonium plus potassium cycle resin ("Resodec").

‡ Intake approximate.

Data are expressed per individual period rather than cumulatively.

EXPERIMENTAL MATERIAL AND METHODS

A carboxylic resin, Amberlite IRC-50, was administered in its ammonium form or in a combination of ammonium and potassium forms (Resodec),* to four patients with congestive heart failure and peripheral edema. During the study in each patient, serum and blood were analyzed at the beginning and end of each period for electrolytes and urea nitrogen. Complete balances were measured daily of chloride, sodium, potassium, and nitrogen, in three of the patients; in one patient, the excreta were analyzed but the intake was only approximated. Sodium and potassium in serum and urine were determined by means of a Barclay internal standard flame photometer,[13] chloride in serum and urine by the methods of Eisenman[14] and Harvey,[15] respectively. Total carbon dioxide content was measured in serum by the method of Stadie and Van Slyke,[16] and nitrogen in urine and feces by macrokjeldahl technic. Representative aliquots of diet and whole stool specimens were digested with concentrated nitric acid and the diluted filtrate poured through the flame photometer for the determination of sodium and potassium. Balances were averaged for three- or two-day periods to eliminate from the results as far as possible the factor of variation in the daily rate of excretion of feces. The two-day periods were necessary in one of the patients, T. M., because of a colostomy irrigation every second day.

* Supplied through the courtesy of Smith, Kline and French Company of Philadelphia.

Results

The results are presented in table 1 and in figures 1 to 4, inclusive.

Exchanges of Sodium and Water. The fecal excretion of sodium was increased in all four of the patients when resin was given (table 1); and in two of the patients (G. B. and T. M.), peripheral edema which previously had been intractable to treatment was eliminated (figs. 1 and 2). During the period when these two patients lost their edema, as much or more sodium was excreted in the urine as in the stools

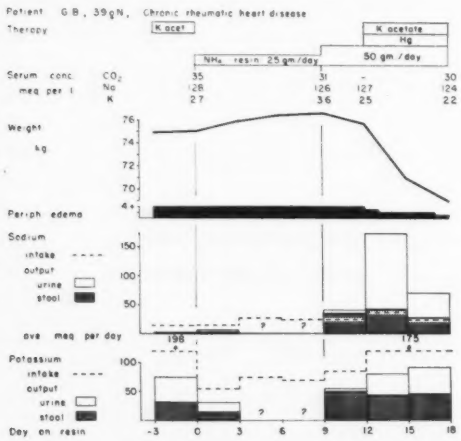

FIG. 1. Resin therapy plus mercurial diuretic resulting in the partial elimination of edema previously refractory to mercurials alone (patient G. B.). During days 10 to 18 inclusive sodium was lost in the stools in amounts equal to or slightly in excess of the intake, but the largest portion of sodium was excreted in the urine.

(mercurial diuretics being administered simultaneously). On three occasions when mercurials failed to act on the kidneys, edema fluid was not eliminated, even though the resin resulted in the fecal loss of sodium in amounts equal to, or somewhat in excess of, the dietary intake of the ion (G. B., fig. 1, days 9–12; J. B., table 1, days 4–12). In only one period in one patient, T. M., in whom the fecal excretion of sodium appeared to be greatly in excess of the dietary intake (fig. 2, days 2–4), did the resin remove endogenous sodium (and in this patient feces were eliminated by colostomy irrigation).

Exchanges of Chloride. Chloride was essentially absent from all of the stools of three of the four patients (table 1). In patient T. M., who had the colostomy irrigations, chloride was present in the stools but in smaller amounts than sodium. However, the *renal* excretion of chloride exceeded that of sodium in all the periods of resin therapy in three patients and in the last period of the other patient (G. B.) (table 1). The excess of chloride over sodium in the urine frequently was greater than the

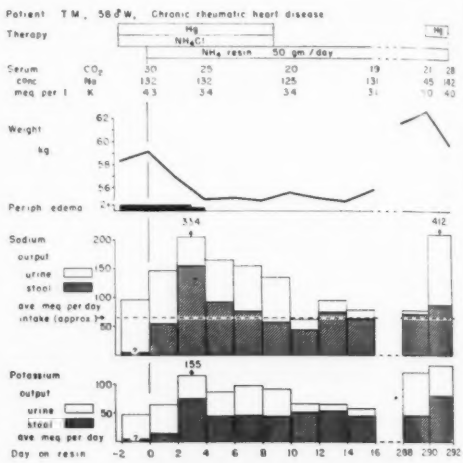

FIG. 2. Resin therapy plus mercurial diuretic resulting in the complete elimination of edema previously refractory to mercurials alone (patient T. M.). On days 3 and 4 the patient lost considerably more sodium in the stool than was ingested, but much of the sodium removed was excreted in the urine. Nine and one-half months later the patient was still responding to the resin and mercurials in the same manner. During the interval the patient had been receiving ammonium plus potassium resin.

excess of sodium over chloride in the stools (fig. 3). Presumably the difference was due to the somewhat larger amount of chloride in the diets. The correlation between these two sets of values indicates in these patients an adequate renal response to the removal of sodium by resin through the intestinal tract.

Exchanges of Potassium. The fecal excretion of potassium was increased following the administration of resin in three of the patients studied (table 1, figs. 1, 2). In those patients in whom exact balances were measured, the fecal loss of potassium did not exceed the total in-

take of dietary potassium or of the ion administered as a salt (acetate) or in the resin (Resodec); that is, the potassium balance did not become negative.

Effect on Serum Electrolyte Concentrations. The concentration of sodium in serum was already below normal limits in two patients and fell to slightly lower levels on resin therapy (G. B., T. M.). In one of these patients, T. M., the serum sodium concentration had returned to the upper limits of normal when the patient was studied again after 288 days of resin therapy (fig. 2). In the other two patients the serum concentration of sodium did not fall below the

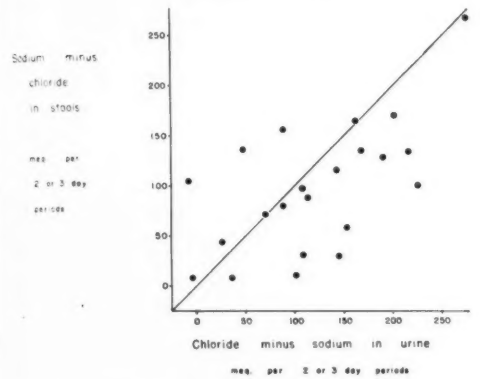

FIG. 3. Relationship of the excretion of sodium and chloride ions in stools and urine during resin therapy. The excess of sodium over chloride in stools correlates well with the excess of chloride over sodium in the urine.

normal range. The serum concentration of potassium was likewise below the normal range in two of the patients before resin therapy was initiated, and in one of these, G. B., the serum potassium fell still further despite the administration of extra potassium acetate and a positive balance of the ion (fig. 1). In patient T. M., the only patient who was treated with ammonium resin without potassium in the resin or supplementing the diet, the serum potassium level fell below the normal range; at the end of 290 days of treatment with ammonium plus potassium resin most of the time, the serum concentration was again normal (fig. 2). The total carbon dioxide content of serum fell below the lower limit of normal (26 mM. per liter) in two of the four patients on resin (fig. 2), and the chloride concentration rose.

Fecal Excretion of Sodium and Potassium. In all but four periods, sodium in the stools exceeded potassium when the ammonium resin was given, the average daily fecal excretion of sodium being between 28 and 156 mEq. (fig. 4). This range of fecal excretion of sodium represents 0.56 to 3.12 mEq. per gram of resin administered. When ammonium plus potassium resin was given less sodium was lost: 4 to 37 mEq. per day (fig. 4) or 0.08 to 1.48 mEq. per

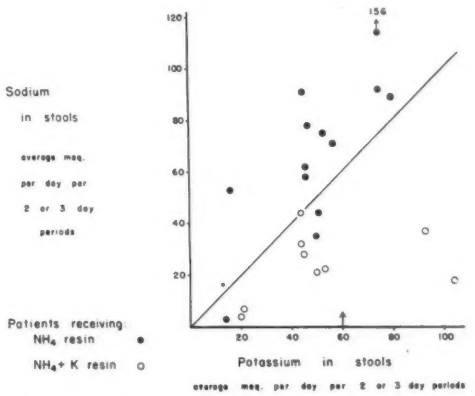

FIG. 4. Relationship of sodium to potassium in the stools during resin therapy. Sodium usually exceeds potassium in stools from patients receiving ammonium resin. The converse is true in those receiving the ammonium plus potassium resin. However, in the majority of periods during which the latter form of the resin was administered, the fecal excretion of potassium did not exceed the daily intake in the resin of 60 mEq. (arrow on abscissa).

gram of resin administered. On this combined form of resin the potassium in the stool exceeded the sodium. In only two periods, however, did the average daily fecal excretion of potassium exceed the amount administered with the resin (60 mEq.).

DISCUSSION

These experiments indicate clearly that a carboxylic exchange resin, when ingested by patients with congestive heart failure, will remove sodium and potassium by way of the intestinal tract. They do not show, however, that the amount of sodium so removed will greatly exceed the sodium in the diet. Only in the pa-

tient whose fecal excretion was obtained by colostomy irrigation was there a significant removal of endogenous sodium. Even in this patient, T. M., as well as in patient G. B. (the two patients whose edema was eliminated following the inception of resin therapy), the major portion of the sodium excreted was excreted in the urine (figs. 1 and 2). Since both of these patients had been partially or completely refractory to treatment with mercurial diuretics and other measures prior to the resin,* it appears that in some way the administration of resin potentiated or activated the mercurial diuretics in these two patients. In the other two patients, L. J. and J. B., this did not occur, and these patients did not lose their edema even though resin was removing sodium from the intestinal tract. Resin may prevent the further accumulation of edema by preventing the absorption of dietary sodium, but it is probably a mistake to consider that it causes the elimination of edema by removing endogenous sodium through the intestinal tract.

The factors which control the uptake of sodium by resin in the intestinal tract need further elucidation. One factor is the form or cycle of the resin which is employed. No evidence has yet been presented of a greater efficiency in sodium removal of hydrogen versus ammonium cycle resin. Our studies indicate that the inclusion of potassium cycle with ammonium cycle resin reduces the amount of sodium which is withdrawn. Another factor, however, is the amount of sodium ingested. Less sodium is taken up by the resin on lower sodium intakes.[17] But increase in the sodium intake quickly overtaxes the capacity of the resin to remove it, as shown by the inability of cardiacs on the resin to take more than 2 to 4 Gm. of sodium chloride without the accumulation of edema.[18] Considering the large turnover of sodium in the intestinal fluids, it is surprising that more exogenous and endogenous sodium is not taken up. There must be much to learn concerning the effect of alterations in visceral circulatory dynamics on intestinal fluid exchanges. Endocrine factors must also be considered. The demonstration of a reduction in fecal sodium removal by resin following the injection of desoxycorticosterone[19] suggests strongly that the cells of the intestinal mucosa may be analagous in some ways to those of the renal tubule.

Another of the unsolved problems is how the ingestion of cation exchange resin may potentiate the action on the kidneys of a mercurial diuretic. An obvious possibility is that a chloride acidosis is produced similar to that resulting from ammonium chloride administration. The difficulties with this hypothesis in explaining the reactions in these particular patients are several. In patients G. B. and T. M. ammonium chloride given prior to the resin did not potentiate the mercurials, and in patient L. J. much less sodium was excreted by the kidneys when resin was given with mercurials than when ammonium chloride was given with mercurials. This was true despite the fact that the serum carbon dioxide content was at its lowest level after the resin rather than after the ammonium chloride. While these studies are not extensive enough to be definitive on this point, they do suggest that other factors enter into the interactions of these two therapeutic agents.

Summary and Conclusions

Electrolyte exchanges were studied in four patients with edema due to congestive heart failure during the administration of cation exchange resin, with the following results:

1. The fecal excretion of sodium and potassium was increased.

2. The pure ammonium resin removed more sodium than the ammonium plus potassium resin.

3. In most periods, the excess of sodium over chloride in the stools was more than equalled by the excess of chloride over sodium in the urine.

4. Except in the patient with the irrigated colostomy, the fecal excretion of sodium did not greatly exceed the dietary intake of the ion.

5. In two of the four patients who were previously refractory to treatment, most or all of their edema was eliminated.

6. The major portion of sodium lost in these

* Previous unsuccessful attempts to treat the hyponatremic edematous state of patient G. B. have been described elsewhere.[20]

two patients was excreted through the kidneys with the concomitant administration of mercurial diuretics.

It is concluded that carboxylic cation exchange resin, given to patients with congestive heart failure, (1) will prevent the absorption of some sodium from the intestinal tract and so promote a negative balance of the ion, and (2) may be a useful adjunct in the treatment of refractory cases by potentiating or initiating the action on the kidneys of mercurial diuretics. The mechanisms and conditions for such potentiation are at present unknown.

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Tissue Cations and Water in Arterial Hypertension

By Louis Tobian, Jr., M.D., and John T. Binion, B.S.

Human hypertensive subjects were found to have an increased sodium and water concentration in renal artery and psoas muscle. Hypertensive rats showed a high water content in their aortas. If the water and sodium content were increased in hypertensive arterioles as well as arteries, the swelling of the arteriolar walls would narrow the lumens enough to account for much of the increased peripheral resistance. Low sodium diets may alleviate hypertension by lowering the sodium and water contents in arteriolar walls toward normal values.

IT IS generally agreed that decreased lumen size of small arterioles is mainly responsible for the high arterial blood pressure in hypertensive disease. Chemical changes in the arteriolar wall undoubtedly play an important part in this process. However, arteriolar tissue samples are difficult to obtain for chemical studies. It was felt that chemical analysis of the larger muscular arteries might give an indication of chemical changes occurring in the arterioles, since both tissues are predominantly made up of vascular smooth muscle, and Wiggers believes that the walls of the larger arteries participate in the hypertensive process.[1] In this study, other tissues were also analyzed in order to compare their chemistry with that of the muscular arteries.

Methods

Specimens of renal artery, psoas muscle, right auricle, bladder, and brain (frontal lobe) were obtained at the autopsy table and wiped free of blood. The adventitia was stripped from the renal arteries, leaving the intimal and medial layers for chemical analysis. Tissues were weighed, dried, defatted, and extracted with 0.75 normal nitric acid according to the method of Lowry and Hastings.[2a] In the sodium determination the sodium was ashed, precipitated, and washed according to the method of Lowry and Hastings,[2b] and determined colorimetrically by the method of Hoffman and Osgood.[3] Potassium was ashed, precipitated, and washed in Vycor tubes as described by Consolazio and Talbott[4] and determined colorimetrically by the method of Shohl and Bennett.[5] Magnesium was determined by the method of Michaels and associates.[6]

Selection of Cases. Cases were classified either in the hypertensive or the normotensive group only when clinical and postmortem data left no doubt about their correct placement.

Results

In renal arteries of hypertensive patients the sodium content of the medial and intimal layers was 22 per cent higher and the water content 17 per cent higher than in arteries of normotensive subjects. (See table 1.)

Psoas muscle showed a 22 per cent higher sodium content and a 15 per cent higher water content in hypertensive patients than in normotensive subjects. These differences were statistically significant. (See table 2.)

There was no significant difference between the normotensives or hypertensives in potassium or magnesium content of arteries or muscle.

The sodium content of the brain in hypertensive patients was found to average 21 per cent higher than in normotensive subjects. However, the number of cases is small and there is one chance in six that the difference is due to chance. (See table 3.)

In right auricle and bladder no significant chemical differences between hypertensives and normotensives were found.

In figure 1 each point represents an individual subject, and the sodium content of renal artery is plotted against the water content. As would be expected from the osmotic activity of sodium, water and sodium contents tended to vary in the same direction.

From the Department of Internal Medicine, Southwestern Medical School of The University of Texas, Dallas, Texas.

L. T., Jr. is an Established Investigator of the American Heart Association.

It is to be expected that tissues would gain sodium after death as a result of diffusion. However, this process cannot account for the increased sodium in the renal artery and psoas muscle of the hypertensive group, since tissues were collected in this group an average of 5.4 hours after death, while tissues of the normotensive group were collected an average of 7.6 hours after death. If anything, the difference in sodium content might be even greater, were it not for the longer period of sodium diffusion after death in the normotensive group. Diffusion of sodium into renal artery tissue would be relatively slow because of the high sodium content of arteries.

The sodium and water content of renal artery and psoas muscle are not well correlated with the presence of edema in these subjects. There were several instances of high sodium and water content in subjects with no edema and instances of low sodium and water content in edematous subjects.

The data give no clue as to how much of the increased sodium and water in hypertensive artery and muscle is intracellular and how much extracellular.

Preliminary results also show that severely hypertensive rats have a 19 per cent higher water content in their aortas than normotensive rats (see table 4). The aorta of the rat has the histologic appearance of a small muscular

TABLE 1.—*Analysis of Human Renal Artery (Media and Intima)**

	Water %†	Composition per 100 Gm. of dry fat-free solids			
		Water Gm.‡	Sodium mEq.‡	Potassium mEq.‡	Magnesium mEq.‡
13 Hypertensives	78.7 (±2.1)	370 (±80)	48.1 (±6.9)	18.9 (±3.2)	3.8 (±0.9)
15 Normotensives	76.0 (±2.3)	316 (±59)	39.5 (±7.1)	18.7 (±3.6)	3.5 (±0.8)
Difference of means	2.7	54	8.6	0.2	0.3
Probability of chance difference between means	.001		.001	.9	.4

* Mean values and standard deviation.

† % Water = $\frac{\text{Wt. of water}}{\text{Wt. of water + wt. of dry fat-free solids}}$

‡ Per 100 Gm. of dry fat-free solids.

TABLE 2.—*Analysis of Human Psoas Muscle**

	Water %†	Composition per 100 Gm. of dry fat-free solids			
		Water Gm.‡	Sodium mEq.‡	Potassium mEq.‡	Magnesium mEq.‡
11 Hypertensives	80.8 (±2.8)	421 (±99)	18.0 (±4.7)	46.5 (±4.8)	8.8 (±1.1)
11 Normotensives	78.5 (±1.8)	366 (±54)	14.8 (±3.1)	44.1 (±4.4)	8.6 (± .7)
Difference of means	2.3	55	3.2	2.4	0.2
Probability of chance difference between means	0.02		.05	.2	.7

* Mean values and standard deviations.

† % water = $\frac{\text{Wt. of water}}{\text{Wt. of water + wt. of dry fat-free solids}}$

‡ Per 100 Gm. of dry fat-free solids.

TABLE 3.—*Analysis of Human Brain (Frontal Lobe)*

	Composition per 100 Gm. of dry fat-free solids			
	Water Gm.*	Sodium mEq.*	Potassium mEq.*	Magnesium mEq.*
5 Hypertensives	641	51.2 (+12)	46.0	5.9
8 Normotensives	629	42.2 (+ 8)	42.5	5.9
Difference of means	12	9.0	3.5	0
Probability of chance difference between means	.8	.16	.5	

* Per 100 Gm. of dry fat-free solids.

artery, being made up predominantly of smooth muscle.

It is of interest that Eichelberger has also found an increase in muscle sodium and water in Goldblatt hypertensive dogs.[7]

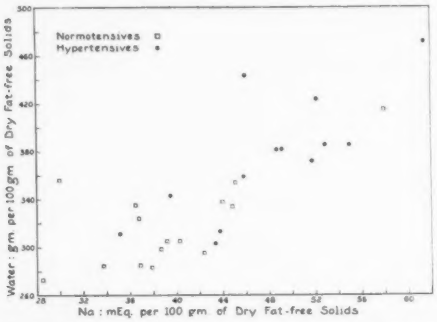

FIG. 1. Relation of water to sodium in the renal arteries of individual subjects.

TABLE 4.—*Water Content of the Aorta of Hypertensive Rats*

(Gm. per 100 Gm. of dry fat-free solids)

Normotensive (Average of 15 rats)	Mild Hypertensive (Average of 8 rats)	Severe Hypertensive (Average of 10 rats)
175	184	208

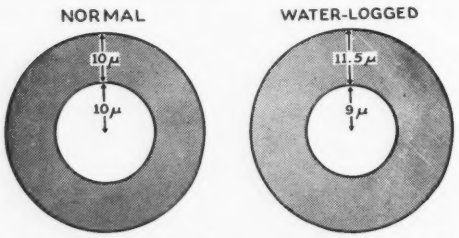

FIG. 2. Dimensions of an arteriole before and after a 13 per cent swelling of the arteriolar wall. The decrease in lumen size would increase flow resistance 54 per cent.

DISCUSSION

It may be worthwhile to speculate about the possible causes and effects of the increased sodium and water content in renal artery associated with hypertension. It is quite possible that the increased water in the hypertensive arterial wall is there because of an increase in the number of intracellular osmotically active particles. This concept of intracellular metabolic alteration readily fits the fact that both artery and psoas muscle showed increased water and sodium contents. An increase in osmotically active intracellular sodium could account for a good part, but not necessarily all, of the increased arterial water content.

If the increased water concentration in hypertensive renal artery were also present in hypertensive arterioles, important results would follow. In the hypertensive renal artery, there was 17 per cent more water for each gram of solids than was found in normotensive renal artery. This amount of swelling with water would increase the mass of solids plus associated water 13 per cent in the hypertensive group.

In figure 2 there is depicted a normal arteriole 40 microns in diameter with a normal wall to lumen ratio of 1:2. If this wall were swelled 13 per cent as a result of more water, the radius of the lumen would decrease from 10 to 9 microns and the wall thickness would increase from 10 to 11.5 microns. According to Poiseuille's equation, which states that flow resistance in capillary tubes varies inversely with the fourth power of the radius, this small decrease in lumen size would increase flow resistance 54 per cent in this hypothetic arteriole. If this were occurring in all the arterioles throughout the body, considerable hypertension would result.

The concept of the arteriolar wall swelled with water fits well with the observed fact that the blood pressure of a hypertensive patient can make large responses to either vasoconstricting or vasodilating stimuli. If the arteriolar muscle were hypercontracted, one might expect that further vasoconstriction would be somewhat limited and vasodilation responses would be disproportionately large.

The wall of the hypothetic "water-logged" arteriole in figure 2 is thickened to about the same degree as the walls of hypertensive arterioles in histologic muscle preparations. In benign hypertensive arterioles the wall to lumen ratio measured on slides averages 1:1.5 compared with a ratio of 1:2 in normotensive arterioles.[8] Similarly, in our hypothetic "water-logged" arteriole, the wall to lumen ratio is 1:1.56 compared to the 1:2 ratio in the "normal" arteriole.

The fact that the renal artery of hypertensive patients contains abnormally large amounts of sodium may explain the effectiveness of drastic low sodium diets in lowering the blood pressure in hypertensive patients. If practically no sodium is supplied in the diet, individuals usually come into sodium balance eventually by a drastic reduction in the urinary sodium excretion. However, the body does lose about 200 mEq. of sodium before this balance is attained.[9] Some of this deficit in total body sodium may be accounted for by a small contraction of extracellular fluid volume and blood volume.[10, 11] However, it seems quite unlikely that this small decrease in the volume of blood and extracellular fluid is the actual cause of the lowering of blood pressure.[11, 12] It is quite conceivable that a significant fraction of the deficit in total body sodium is lost from the walls of arteries and arterioles. As sodium was being lost from the arteriolar walls, the water osmotically bound by that amount of sodium would also be lost, provided other substances remained unchanged. As outlined above, this would effectively increase the lumen size of arterioles and thus decrease the level of arterial blood pressure.

Moreover, this concept may be applied in reverse. Sapirstein, Brandt, and Drury have reported hypertension in rats allowed to drink only a 2 per cent sodium chloride solution.[13] Lenel, Katz, and Rodbard have reported an elevation of blood pressure in chickens on a high sodium intake.[14] McQuarrie and coworkers have produced definite hypertension in children during periods of feeding 30 to 60 Gm. of salt daily.[15]

In all these cases, the high sodium intake could be increasing arteriolar sodium and water contents with resulting narrowing of the arteriolar lumens and arterial hypertension.

The concept also fits in with our previous experiments on bilaterally nephrectomized rats.[16] Sixty-four per cent of these rats developed hypertension three days after bilateral nephrectomy, provided that they had free access to sodium in the diet. If sodium was withheld from the diet the day before and three days after the bilateral nephrectomy, hypertension appeared in only 2 per cent of the rats, even though there was no chance for these rats to become significantly depleted of sodium. It would appear that deficiency of the "renal anti-hypertensive function" cannot readily produce hypertension in these rats, unless sodium is supplied in the diet. Absence of sodium in the diet may prevent this type of hypertension by preventing an increase in the amount of arteriolar sodium and its osmotically bound water.

Raab and his associates[17] have also shown that a low salt diet decreases the pressor response of hypertensive patients to norepinephrine and epinephrine. The elevated sodium in hypertensive artery may not only cause swelling of the wall with water, but may also make the artery more responsive to a given intensity of sympathetic vasoconstrictor nerve impulses.

Alterations in adrenal cortical steroid metabolism may or may not play a role in causing the elevated sodium and water in hypertensive artery and muscle. However, it is well known that hypertension produced by desoxycorticosterone can be prevented by a drastically low sodium diet and augmented by a high sodium diet. This type of hypertension is mainly "humoral" and not neurogenic.[18] In view of the strong influence of dietary sodium in this type of hypertension, it is quite conceivable that the walls of the peripheral arterioles contain excessive sodium and water, which would lead to increased peripheral resistance and hypertension. Moreover this same speculation would apply in the hypertension of toxemia of pregnancy, which is also markedly influenced by changes in the level of dietary sodium.

In the hypertensive subjects, the increased lateral hydrostatic pressure in the lumen of arteries undoubtedly increases the rate of fluid circulation from the lumen outward through the walls of the arteries. However, there is no reason to think that this heightened rate of circulation increases the amount of extracellular fluid in the walls of arteries. Moreover, the spaces between cells are not visibly widened in hypertensive arteries as they should be if there were considerable increases in extracellular water.

SUMMARY

1. Human hypertensive subjects showed an increased sodium and water concentration in renal artery and psoas muscle.

2. Preliminary results show that hypertensive rats have a high water content in their aortas.

3. The possible relationships between the above facts and arteriolar narrowing in hypertension are discussed.

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Heart Failure and Pulmonary Edema Produced By Certain Neurologic Stimuli

By Robert Paine, M.D., John R. Smith, M.D., Harvey R. Butcher, M.D. and Frank A. Howard, M.D.

Experimental evidence has indicated that the genesis of acute pulmonary edema due to insufficiency of the left ventricular myocardium is dependent upon pulmonary engorgement and rapid filtration of fluid from the capillaries. It has been possible to demonstrate that significant elevation of arterial blood pressure from noxious stimulation of the central nervous system may be poorly tolerated when the myocardium has been previously damaged, so that acute left ventricular failure has occurred. The resulting massive pulmonary edema clearly followed the hemodynamic changes of severe congestion.

NUMEROUS clinical and experimental observations have indicated that acute pulmonary edema occurs from left ventricular insufficiency when cardiac venous inflow and right ventricular function remain adequate. Pulmonary transudation then occurs because of rapid filtration of fluid from the capillaries into the alveolar spaces. On the other hand, the occasional occurrence of fulminating pulmonary edema in patients with injury or other disease of the central nervous system, and unassociated with recognizable heart failure, has raised the question of other mechanisms in the genesis of lung edema.[1] Therefore, many workers have considered the possibility of a "neurogenic" pulmonary edema of reflex origin from cerebrospinal disease and abnormal autonomic function.

The "neurogenic" concept of lung edema formation has been supported by a number of experimental studies. The administration of adrenaline to rabbits has been repeatedly observed to evoke pulmonary edema.[2–4] Similarly, experimental lead poisoning, large intravenous or intra-arterial blood or saline infusions, hypoglycemia, and injury of the central neural tissues have been shown to provoke pulmonary edema in experimental animals.[5–13] Unfortunately, these studies were carried out without critical evaluation of cardiovascular performance during the formation of pulmonary edema, so that the concept of "neurogenic" lung transudation does not appear to be supported by sound experimental evidence.

The neurogenic mechanism of pulmonary edema has been seriously questioned by observers who have studied cardiovascular function in relation to lung congestion and transudation.[14–19] Paine and his associates demonstrated that fluid exchange in the lungs follows the Starling principles of fluid balance.[14] They showed that, in the course of pulmonary congestion the elevation of capillary pressure in excess of osmotic tension rapidly forced fluid into the alveolar spaces. Conversely, when osmotic tension was sufficiently lowered by the depletion of plasma proteins in a normally functioning circulation, transudation likewise occurred from unopposed normal capillary filtration. These authors were able to provoke pulmonary engorgement and edema by impairing the function of the left ventricular myocardium in various ways. It has also been demonstrated that experimental pulmonary edema accompanying acute heart failure may

From the Cardiovascular Division, Department of Medicine and the Department of Surgery, Washington University School of Medicine and the Oscar Johnson Institute for Medical Research, St. Louis, Mo.

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be abolished by drugs which improve cardiac function.[15]

The available evidence, largely summarized by Paine and his co-workers,[14] suggests that autonomic stimulation of critical degree, or autonomic stimuli arising from injury or other disorders of the central nervous system, may lead to severe derangements of cardiovascular function. If the derangement is such as to overload the left ventricle, pulmonary congestion and edema will ensue. Experiments concerning disorders of cardiovascular performance in relation to aberrant neurologic mechanisms will be reported in this communication.

TABLE 1.—*Effects of Epinephrine in Open-Chest Dog Preparations*

Exper. No.	B.P. Before	B.P. After	P.A. Before	P.A. After	L.A. Before	L.A. After	Rate Before	Rate After	Pulm. Edema
12	135	190	22	24	12	13	176	180	Absent
23	95	210	20	40	13	34	184	120	Absent
25	120	230	22	64	14	88	124	174	Present
27	135	280+	38	65	13	90	200	168	Present
31	115	280+	30	40	16	38	156	144	Absent
33	120	205	24	36	20	13	168	252	Absent
57	125	270	24	38	15	22	168	156	Absent
58	110	280	20	30	10.5	35	172	250	Absent
59	115	250	24	35	11.5	45	160	140	Absent

B. P., P. A. and L. A. represent mean blood pressure, pulmonary arterial pressure and left atrial pressure in mm. Hg or cm. of water. "Before" and "After" indicate before and after 0.25 mg. doses of adrenaline.

METHODS

All of the experimental procedures were carried out on dogs under Nembutal anesthesia. Respiration was maintained by a Starling pump attached to a bayonet cannula securely ligated into the trachea. The thorax was opened by longitudinal sternal division, and the preparation was heparinized. Pulmonary arterial pressure was obtained by ligation of a small glass cannula into a branch of the right upper lobar artery with connection by flexible tubing to a conventional mercury manometer. Pulmonary venous tension (as reflected by left atrial tension) was secured by means of a cannula and water manometer attached to the left auricular appendage. Systemic arterial pressure was recorded from one of the femoral arteries using a mercury manometer. Adrenaline was usually administered through the tubing directly into the atrial cavity.

In another group of experiments, acute left ventricular strain was produced by the creation of severe aortic insufficiency by means of valvulotomy. The right common carotid artery was isolated and ligated. A long genitourinary biopsy forceps, with rounded blunt jaws, was then introduced through the artery and into the ascending aorta to the level of the aortic valves. It was not difficult to ascertain the position of the instrument in relation to the valve leaflets, and any one of the cusps could be tightly seized by the blunt jaws and torn from its attachment. It was seldom possible to destroy more than one leaflet of the valve without precipitating immediate and fatal heart failure.

Severe hypertension from injury to the central nervous system was induced by barium sulfate embolism of the brain. For this procedure the right common carotid artery was ligated at its midpoint in the neck; a suspension of 5 per cent barium sulfate in saline was injected through a cannula previously ligated distally into the vessel in cephalic direction. After injection of the suspension, the material was washed into the cephalic circulation with 5 to 8 cc. of whole blood. Embolization of the cephalic circulation was combined with valvulotomy in another series of experiments. Both procedures were readily carried out through the right common carotid vessel.

RESULTS

Effects of Adrenaline on Cardiopulmonary Dynamics. Nine experiments were performed on nine dogs. Under conditions of opened thorax with positive pressure respiration, mean pulmonary arterial pressure varied in most experiments from 20 to 30 mm. Hg, and left atrial pressure ranged from 10.5 to 16 cm. of water. Control systemic blood pressure was recorded as 95 to 135 mm. Hg mean.

The injection of 0.25 mg. of adrenaline through the left atrial cannula provoked transient hypertension and tachycardia without exception. The hypertension attained or exceeded levels of 230 mm. Hg in all but two instances, and pulmonary venous and arterial pressures were also variably elevated (see table 1). With the exception of two experiments, biopsy of the lung tissue showed no convincing evidence of alveolar transudation on gross or microscopic section.

In two experiments (experiments 25 and 27), pulmonary congestion was clearly evident during the strains imposed by adrenaline. In one,

experiment 27, the pulmonary arterial pressure was initially elevated. These two preparations responded to adrenaline (0.25 mg.) with marked increases in pulmonary venous and arterial pressures. Pulmonary edema was grossly evident on biopsy, and was confirmed by microscopic study. Dilatation of the heart was observed in the course of the experiment.

The outcome of experiment 33 was of some interest, although it involved a technical error. After control observations and the administration of adrenaline, the atrial cannula was inadvertently loosened so as to allow a free escape of blood from the appendage. Marked hypertension occurred as an adrenaline effect, but increased pulmonary venous pressure was prevented by the rapid run-off of blood from the venous circuit and vascular pressures in the lungs were not elevated. Edema, of course, was not found.

This experimental evidence suggests that only when myocardial function was adequate under the conditions of hypertensive strain was congestion of the lungs absent. When elevation of pulmonary vascular pressures appeared following adrenaline, there were indications of loss of left ventricular output capacity and edema of the lungs occurred. In the latter instances, the causes of myocardial insufficiency invoked by adrenaline were not apparent.

Adrenaline in Dog Preparations with Aortic Insufficiency. Six experiments were performed on six dogs. After control observations of the open-chest preparation were made, aortic valvulotomy was carried out. The establishment of aortic insufficiency was signalized by immediate moderate enlargement of the left ventricle and a conspicuous increase in the force of cardiac contraction. A loud aortic diastolic murmur, frequently associated with a diastolic thrill, was noted over the entire heart. A striking waterhammer pulse invariably occurred. The production of the valvular defect did not materially alter heart rate. However, in four instances mean arterial blood pressure gradually declined to levels of shock; in two, arterial tension was maintained at normal values. In all cases the excursions of the mercury column were augmented. Pulmonary venous and arterial tensions continued within normal range. In spite of the fact that shock occurred in four of the preparations, it was assumed that a sharp elevation of arterial tension, regardless of the control level, might operate as a critically added strain to the previously damaged heart and thus lead to the production of congestion of the lung. This assumption proved to be correct as indicated in table 2.

When circulatory equilibria after aortic regurgitation were assured, 0.25 mg. of adrenaline was administered through the atrial tube. Adrenaline produced a prompt rise of arterial blood pressure in each experiment. However, the blood pressure did not rise to high levels in the animals that were initially in shock. Nevertheless, each preparation exhibited marked pulmonary congestion with edema, manifested by elevation of pulmonary vascular pressures following the strain induced by adrenaline. Conspicuous dilatation of the heart was noted in all instances.

TABLE 2.—*Effects of Adrenaline on Animals Previously Subjected to Aortic Valvulotomy, and with Aortic Insufficiency*

Exper. No.	B. P. Before	B. P. After	P. A. Before	P. A. After	L. A. Before	L. A. After	Pulmonary Edema
69	20	80	8	65	15	80	Present
70	45–60	130	18	48	28	80	Present
71	100	170	10	38	16	62	Present
72	50	75–80	20	40	19	50	Present
73	30	140	20	65	17	80	Present
74	100–110	210	20	55	15	80	Present

Symbols as in table 1.

In all of these experiments the administration of adrenaline precipitated pulmonary edema when the hearts had been previously damaged. The presence of vascular collapse did not preclude the occurrence of disastrous failure of the myocardium when the blood pressure was elevated to levels usually considered moderate. Again, pulmonary edema appeared with congestion of the lung tissue.

Effects of Embolic Injury of the Brain. The previous observations indicated that severe sympathetic stimulation may cause myocardial failure, especially when the heart muscle has been previously injured. Therefore, it seemed logical to study some of the cardiovascular

effects of abnormal autonomic stimuli from injury of the central nervous system.

Six experiments were carried out on six dogs as described under "Methods." When control observations were completed, 0.5 cc. of 5 per cent barium sulfate suspension was injected cephalad into the right common carotid artery and washed in with whole blood. The injection was followed immediately by a mild, evanescent tonic convulsion and subsequent relaxation of the animal. In all instances there was a prompt rise of arterial blood pressure and the occurrence of bradycardia, with a moderate decrease of heart rate. The hypertensive reaction was transient in each case, and both the hypertension and bradycardia invariably subsided in 6 to 10 minutes. Actual elevations of blood pressure were less extreme than from 0.25 mg. doses of adrenaline, and in all instances attained mean levels of 165 to 230 mm. Hg. Pulmonary venous and arterial pressures were not significantly changed with the exception of one experiment where pulmonary venous tension rose from 8.5 to 32 cm. of water and mean pulmonary arterial pressure increased from 24 to 32 mm. Hg. Minimal edema was thought to be present on section of the lung. Lung biopsies from the remaining uncongested lungs showed no transudation.

TABLE 3.—*Effects of Cerebral Embolism on Animals Previously Valvulotomized and with Aortic Regurgitation*

Exper. No.	B.P. Before	B.P. After	P.A. Before	P.A After	L.A. Before	L.A. After	Rate Before	Rate After	Pulmonary Edema
76	80	40	10	35	14	60			Present
77	140	220	20	65	14	80	224	200	Present
86	105	230	12	50	13.5	73	168	144	Present
87	40	160	10	48	18	61	120	168	Present
88	90	150	16	32	9	45	144	96	Present
89	95	200	16	32	10	39	144	96	Present

Symbols same as table 1.

Production of Marked Pulmonary Congestion in Animals with Aortic Valvulotomy and Cephalic Embolization. These observations were carried out on six animals. As in the preceding cases, these preparations exhibited slight cardiac dilatation following valvulotomy, together with waterhammer pulse and the other manifestations of aortic regurgitation. Arterial blood pressure declined to shock level in one of these animals; normal arterial tension was sustained after valvulotomy in the remainder. Pulmonary vascular pressures were likewise within normal limits following the creation of the valve defect. Without exception, these animals showed violent circulatory changes during particulate embolism of the cephalic vessels (*cf.* table 3). In all of the cases, with the augmentation of arterial tension (and depression of heart rate), there was striking dilatation of the myocardium and a sharp elevation of the left atrial pressure. Left atrial distension was followed almost simultaneously by pulmonary arterial hypertension. The lungs became turgid and voluminous and large rhonchi were audible some distance away. Biopsy of the lung showed intense transudation. The overwhelming heart failure was tolerated only briefly as shock and death quickly ensued. It should be emphasized that under the conditions of myocardial strain imposed by aortic valvulotomy, the function of a number of these hearts deteriorated under moderate increases of blood pressure. It would appear that the degree of hypertension necessary to impose the critical point of myocardial overload might vary depending upon the severity of strain from aortic insufficiency and upon other possible conditions intrinsic to the heart muscle.

COMMENT

From the data offered in these experiments, it would appear that the genesis of pulmonary edema is referable to incomplete function of the left ventricular myocardium which involves failure of optimum removal of pulmonary venous blood. Under these conditions, continued adequate performance of the right ventricle, together with an abundant venous return to the heart, lead to pulmonary engorgement and severe alveolar transudation resulting from rapid capillary filtration.[14] Regarding the present study, the evidence suggests that the heart may be greatly burdened from the hypertension induced by adrenaline, but that heart failure does not always occur. However, when the heart was previously damaged by the creation of (acute) aortic insufficiency, the superimposi-

tion of hypertension and marked tachycardia from epinephrine became intolerable with resultant breakdown of cardiac function and induction of congestion and edema of the lungs.

The occurrence of hypertension following cerebral damage from particulate embolism is of some interest. Many years ago, Cushing[20] published his well-known observation that cerebral compression provoked a rise of systemic blood pressure of a magnitude sufficient to overcome the loss of cerebrovascular irrigation from the external force of compression. The work implied that cerebral ischemia may be directly concerned in the elevation of blood pressure following cephalic trauma or failure of vascular function. Houssay and Molinelli[21] suggested that injury (*piqûre*) of the floor of the fourth ventricle may result in hypertension by inciting a reflex discharge of epinephrine. Years later, Dixon and Heller[22] demonstrated that the injection of kaolin in the region of the medulla oblongata produced a rise of intraventricular tension with resultant elevation of systemic blood pressure. This study again affirmed the observations of Cushing. Similarly, other workers[10, 19] noted that damage to the medulla by fibrin mixtures regularly invoked hypertension, although increased intracranial pressure was said not to occur.[10] A number of investigators have recorded transient hypertension resulting from stimulation of the cerebral cortex[23] and from ischemia of the central nervous system.[24, 25] Taylor and Page[26] were able to induce hypertension in dogs for varying periods by a variety of injurious stimuli to the brain, including ischemia and intense diathermic heat localized about the brain stem. The work of Villaret and his associates[27] is likewise of interest. They embolized the cerebrovascular system with particulate material and observed the occurrence of hypertension, and frequent bradycardia, from the insult. In our experiments, comparable effects from miliary cerebral embolization were evident. The particulate matter was presumably widely disseminated throughout the cerebral vasculature, and the assumption is made that multiple foci of cerebral ischemia may lead to hypertension from stimulation of central autonomic centers.[24–26]

As with the experiments employing adrenaline, the hypertension from cerebral injury may be equally pernicious when the load is thrown upon the damaged heart. It was noted again that, under hypertensive strain, pulmonary congestion did not occur *unless there were indications of myocardial insufficiency and augmentation of vascular pressures of the lungs.* The drastic, moderate, or even slight elevations of blood pressure appeared to be sufficient in the presence of aortic regurgitation to cause severe cardiovascular strain. Nevertheless, it is also possible that the sudden bradycardia occurring in some experiments from neural damage was also instrumental in diminishing left ventricular output, and flooding the lungs. In experimental animals, pulmonary edema has been shown to occur following extreme cardiac slowing and death from acetylcholine,[28] and observations on the controlled circulation[29] have likewise demonstrated striking restrictions of cardiac output from marked diminution of heart rate. Presumably, if abrupt bradycardia occurs with continuing optimum venous return of blood to the right ventricle, the resulting fall of minute output and ensuing impedance of escape of pulmonary venous blood may enhance vascular congestion of the lungs.

A consideration of even greater importance is the mechanism by which venous blood is made available to the right ventricle, in the face of diminishing stroke output of the left ventricle. Under the conditions of these experiments and those reported before[14] the faltering of left ventricular function, brought about by any means, resulted in pulmonary congestion because of the probable abundant venous return and right ventricular competence. The availability of venous blood in heart failure has been explained on the basis of increased blood volume or by increased venous constriction occurring as a part of a general augmentation in vascular resistance.[30] However, it has been exceedingly difficult to achieve salt and water retention in the dog, as the animal appears to have an efficacious mechanism for excess sodium elimination. Also these experiments were of such brief duration that retention of water could scarcely occur. Therefore, it seems improbable that water retention and a consequent increase in blood volume are concerned in the

continuance of high venous return in these experiments. Although the alternative hypothesis of increased venous constriction as a means of hastening the flow of capillary-venular blood has not been proved,[30] it seems to explain most readily the carriage of blood from arteries to veins in the face of a falling left ventricular output.

The data secured from these experiments, as well as from others previously quoted, appears to warrant the conclusion that certain stresses may lead to cardiovascular failure through *neurogenic* mechanisms. When heart failure occurs from these stresses, the resulting pulmonary edema is *cardiogenic*. The data do not permit the assumption that direct neurogenic effects upon the lungs are concerned in the pathogenesis of pulmonary edema.

Summary

A resume of the experimental evidence concerning the mechanism of pulmonary edema from heart failure has been presented. The concept best supported by the evidence indicates that pulmonary edema results from engorgement of the lungs and rapid capillary filtration of fluid as a result of left ventricular insufficiency. The hypothesis that direct neural effects upon the pulmonary vasculature may cause pulmonary edema was examined as follows:

In open-chest preparations of dogs, systemic arterial pressure together with pulmonary venous and arterial pressures were measured by appropriate manometry. The administration of adrenaline or embolization of the cerebral circulation by barium sulfate crystals provoked transient severe hypertension, with tachycardia and bradycardia respectively. Evidence was obtained that normal heart muscle may withstand the hypertensive strain thus produced, since in most preparations the pulmonary vascular pressures were not sufficiently altered to cause pulmonary transudation. In occasional seemingly normal animals, the hypertension from these procedures produced functional staggering of the left ventricle, and when subsequent elevation of pulmonary vascular tensions occurred, alveolar transudation resulted. When the hearts of animals had been previously damaged by aortic valvulotomy so as to cause aortic insufficiency, the vascular strains imposed by epinephrine or by miliary cerebral ischemia regularly caused left ventricular failure. The subsequent events of myocardial dilatation, and augmentation of pulmonary vascular pressure and intense edema of the lungs were invariably outspoken. No evidence was obtained that direct neurogenic effects upon the lungs were concerned in the formation of pulmonary transudation.

It is concluded from these experiments that although stresses against the damaged myocardium may be of neurogenic character, the generation of pulmonary edema is due to a cardiogenic mechanism.

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Death in Potassium Deficiency

Report of a Case Including Morphologic Findings

By JOHN D. KEYE, JR., M.D.

Autopsy of a patient with the sprue syndrome dying in hypokalemia revealed the myocardial and renal lesions of potassium deficiency. Similar renal changes are described under various names in the recent literature. It is suggested that they result from potassium deficiency since they occurred in patients who died with disorders commonly associated with electrolyte imbalance.

THE CLINICAL manifestations of potassium deficiency have been studied extensively,[1–4] but only a few observations concerning the morphologic changes in patients with this ion deficiency are recorded. For this reason, it may be of interest to describe the findings encountered at autopsy in a patient who died with potassium deficiency and steatorrhea of undetermined etiology.

REPORT OF CASE

First Admission (Feb. 23, 1950 to April 22, 1950).

A 37 year old Negro janitor was admitted for investigation of a change in bowel habits and vague abdominal complaints.

History. In November, 1949, he first experienced excessive flatus and a frequent urge to defecate. His stools were said to be soft and of the usual color. Postprandial nausea and emesis were noted later. The vomitus consisted of the fluid imbibed with or without a small amount of food. The symptoms continued and he soon noted the onset of lower abdominal aching, cramping pain. This would come "in spells" and was associated with tenesmus. His appetite diminished; he became weak, and lost 10 to 15 pounds during the month of January. By February, 1950, the patient had to stop work and remain in bed most of the time. Later he began to have five or six loose, watery bowel movements each day. When hospitalized he had lost approximately 30 pounds.

The family, social, and past histories and the review of systems were noncontributory.

Physical Examination. The temperature was 98 F., pulse 88, and the respirations 16 per minute. He was an asthenic Negro, appearing chronically ill, with evidence of recent weight loss. No abnormal pigmentation of the skin or mucous membranes was seen. Examination of the eyes, ears, nose, mouth and chest was not contributory. The abdomen was scaphoid; slight abdominal tenderness without rebound tenderness was noted but no palpable organs, masses or free fluid were detected. Peristalsis was quiet except for periodic rushes associated with the cramping pain. Rectal examination was not remarkable and yellow stool was noted on the examining finger. Both testes appeared atrophic. The cremasteric reflexes were absent bilaterally.

Laboratory Studies. Periodic determination revealed the hemoglobin to vary from 12 to 14 Gm., the red blood count from 3.8 to 6.2 million per cu. mm., the hematocrit from 37 to 52 per cent packed red cells, the sedimentation rate from 4 to 10 mm. in one hour (Westergren), and the white cell count from 4,200 to 10,500 cells per cu. mm. with an essentially normal differential count on four occasions. The red cells were normocytic, and their indexes were within normal limits. Bone marrow studies showed a cellular marrow with no abnormal cells or megaloblastic changes. The urine was negative. The fasting blood sugar was 77 mg. per 100 cc., cholesterol 147 mg., and total protein determinations varied from 6.7 to 7.4 mg. The serum potassium determination was 3.58 mEq. per liter, and the calcium 9.5 mg. per 100 cc. Congo red test showed 69.8 per cent of the dye remaining in the patients serum at the end of one hour. Pancreatic function studies on duodenal drainage, before and after stimulation with secretin and Mecholyl, were within normal range. The serum amylase was 149 units, and the serum lipase 0.55 units. The glucose tolerance test was normal. The serum Kahn test was negative. The icterus index was 4. Using x-ray film the stool test for trypsin was positive. Repeated examinations of the stool for ova and parasites, and cultures for pathogenic bacteria were negative. Fat balance studies revealed 45 per cent of the dry weight of the feces to be fat, with a total nitrogen of 3.3 Gm. per 100 Gm. of feces. Proctoscopy was negative on two occasions.

Roentgenologic Studies. Gastrointestinal roentgenologic study showed a bowel pattern as seen in deficiency syndromes, with a normal esophagus, stomach and duodenum as well as a diverticulum of the sigmoid colon. A chest film, flat plate of the abdomen, and gallbladder series were normal.

From the Departments of Pathology, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Ga.

Hospital Course. Throughout the two months hospital stay the cramping, abdominal pain persisted with at least three to six large, bulky, foul-smelling stools per day. An attempt to control his abdominal discomfort by the use of atropine and mild sedatives was unsuccessful. The symptoms increased after meals. He continued to have marked anorexia. The patient was given a high carbohydrate, low fat diet with supplementary vitamins, intramuscular injections of liver, and also capsules of Tween 80, but no significant improvement occurred. The clinical impression was steatorrhea of undetermined origin.

Interval. The patient was followed in the medical clinic. He continued to lose weight, felt weak and had at least three to four bulky bowel movements each day.

Second Admission (June 12, 1950 to June 19, 1950).

The patient was readmitted for further evaluation. The physical examination was unchanged except for a more apparent weight loss.

Laboratory Studies. The hemoglobin was 10.6 Gm. per 100 cc., and the serum cholesterol 112 mg. The white blood count was 6,900 cells per cu. mm. There was 1 plus albuminuria on three occasions, and asymptomatic, microscopic hematuria which varied from 4 to innumerable red blood cells per high powered field.

Roentgenologic Findings. The small bowel was not remarkable aside from a nonspecific "deficiency pattern."

Hospital Course. Surgical exploration was considered but not attempted. The patient was discharged on the same diet and medications with the addition of pancreatin.

Interval. In the clinic intravenous pyelograms, made to determine the cause of hematuria, were normal.

Third Admission (Nov. 8, 1950, died Nov. 11, 1950).

The patient was again admitted because of extreme weakness and lethargy.

Physical Examination. The temperature was 96 F., the pulse 54, and the respirations 10 per minute. The blood pressure was 94/60. The only change noted was extreme emaciation.

Laboratory Studies. The hemoglobin was 12.1 Gm. per 100 cc., the red cell count 4.61 million cells per cu. mm., the hematocrit 45 per cent packed red cells, normal indexes, sedimentation rate 12 mm. in one hour (Westergren), white cell count 9,950 cells per cu. mm. with 92 segmented forms and 8 lymphocytes. Two eosinophil counts were reported as no cells per cubic millimeter. The urine pH was 5.0 with a specific gravity of 1.000, a trace of albumin, sugar negative. A few granular and hyaline casts were noted on microscopic examination. The total base was 134.7 mEq. per liter, serum sodium was 122.8 mEq., and serum chlorides 102 mEq. The nonprotein nitrogen was 45 mg. and the total proteins 4.67 mg. per 100 cc.

Hospital Course. The patient became progressively weaker and was unable to take nourishment. It was necessary to supplement his intake with parenteral fluids. It was thought that his weakness could not be explained on the basis of low serum sodium alone and potassium deficiency was considered. The patient died before electrocardiograms could be taken. It was noted that he could not breathe unless his head was held extended but potassium replacement therapy was not instituted. The terminal stage developed rather suddenly following an intravenous infusion with five per cent glucose in normal saline and he died with complete flaccid paralysis. The serum potassium run in duplicate, "less than 1.25 mEq. per liter," was reported after death.

Autopsy

Gross Findings. The body showed marked emaciation. The mucosa of the small and large intestines, with the exception of the appendix and rectum, revealed many irregularly distributed, shallow ulcers up to 7 cm. in diameter. These were most numerous in the terminal ileum. The dilated stomach contained about 500 cc. of yellowish, mucoid material. Its mucosa appeared normal. The mesenteric lymph nodes were enlarged, soft, pale, and fleshy.

The heart weighed 210 Gm. (normal 323 ± 40 Gm.), and was not dilated. The valves and the reddish-tan myocardium, as well as the coronary vessels and their ostia, were not remarkable.

The kidneys (combined weights 342 Gm.) showed a smooth outer surface. On cut surface the 7 mm. cortex was pale and the medullary striations were not prominent. The remainder of the urinary tract, as well as the prostate and seminal vesicles were not remarkable.

Additional findings were ascites (150 cc.), bilateral hydrothorax (15 cc. each side), and a left hydrocele. There was no atherosclerosis. The liver (1,090 Gm.) showed no fatty metamorphosis. The lungs (380 Gm. each), esophagus, spleen (98 Gm.), pancreas (90 Gm.), biliary system, adrenals (combined weight 10 Gm.), bone, bone marrow, and musculature were not remarkable. Because of restrictions only a segment of the lumbar spinal cord, and a fragment of the thyroid were removed, and appeared normal.

Histologic Findings. The ventricular myocardium alone revealed a marked, diffuse, interstitial infiltration by neutrophilic polymorphonuclear leukocytes, lymphocytes, and large mononuclear macrophages (fig. 1). Some myocardial fibers near the infiltrates showed necrosis, and occasional naked sarcolemma sheaths were seen (fig. 2). The muscle fibers contained much brown pigment in the paranuclear position, but no demonstrable fat. The pericardium, valves, endocardium, and blood vessels were not remarkable.

The kidneys revealed marked vacuolization of the

Fig. 1

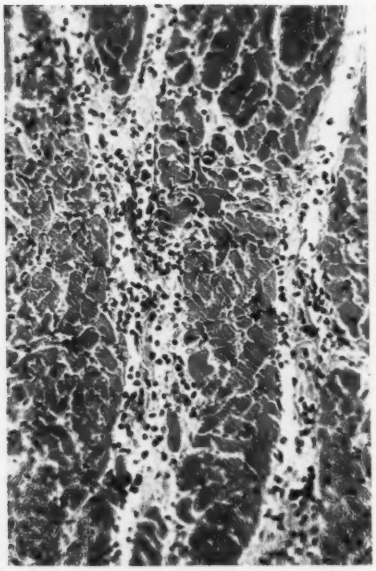

Fig. 2

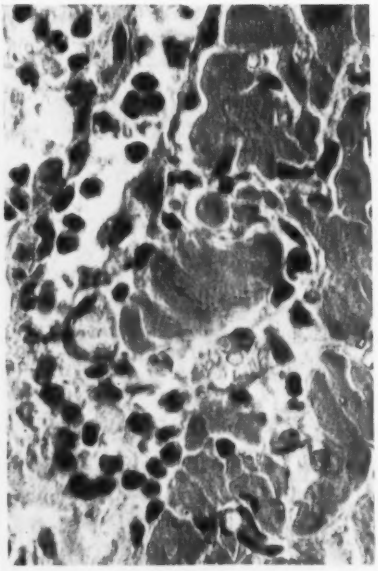

Fig. 3

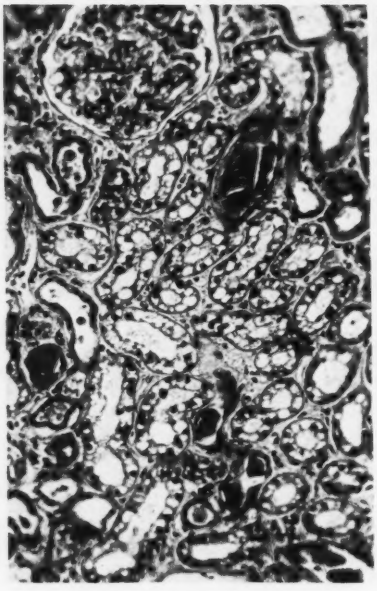

Fig. 4

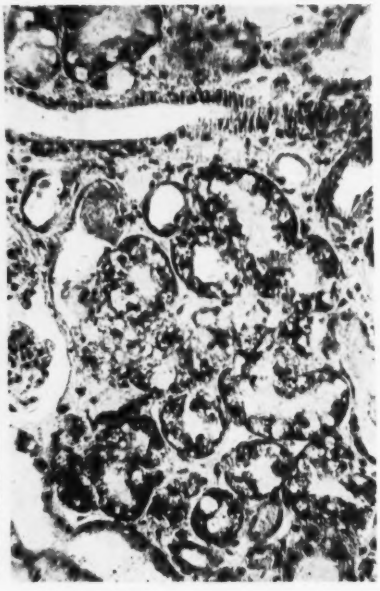

FIG. 1. Interstitial myocarditis. The inflammatory cell infiltration involves primarily the septa. Hematoxylin-phloxine; × 210.

FIG. 2. Interstitial myocarditis. The muscle bundle in the center reveals a smudged cytoplasm, indicative of necrosis. Hematoxylin-phloxine; × 840.

FIG. 3. Tubular nephritis. Note the marked vacuolization of the tubular epithelium. Some tubules contain dense hyalin casts. Hematoxylin-phloxine; × 210.

FIG. 4. Fatty metamorphosis of the renal tubular epithelium. The dark granules represent stained lipid. Note that not all vacuoles contain fat. Sudan IV stain; × 420.

tubular epithelium, chiefly in the proximal convoluted, and, to a lesser degree, in the distal convoluted tubules (fig. 3). The vacuoles varied in size and in their location within the cells. Many of the vacuoles found in the subnuclear position in the proximal convoluted tubules contained fat (fig. 4). The majority of the vacuoles in a supranuclear position failed to stain for fat or glycogen. Occasional necrosis and shedding of the tubular epithelium was noted. The tubules contained much granular acidophilic material and some hyaline casts. The glomeruli, blood vessels and interstitial tissue were not remarkable.

The ulcerations in the small and large intestines reached the submucosa and revealed marked subacute and chronic inflammation. Lipid deposits were not demonstrable in the intestinal wall or in the mesenteric lymph nodes.

The liver showed slight congestion and minimal necrosis of liver cells in the central lobular areas. The liver cells throughout revealed a shrunken, granular, acidophilic cytoplasm. They contained much brown pigment which did not stain with iron stain. Sudanophilic material was absent.

Additional findings were pulmonary edema and congestion, as well as lipoid depletion of the adrenals.

Final Anatomic Diagnoses. Interstitial myocarditis and tubular nephritis consistent with hypopotassemia; ulcerations of small and large intestines consistent with idiopathic sprue; congestion of viscera; ascites, 150 cc.; hydrothorax, bilateral, 15 cc.; pulmonary edema; lipoid depletion of adrenals; emaciation; brown atrophy of liver; hydrocele, left.

Comment

The diagnosis of potassium deficiency in this patient is based upon the appearance of a terminal, flaccid paralysis resulting in respiratory death, an extremely low serum potassium level, and the autopsy findings of marked interstitial myocarditis and tubular nephritis. The ion deficiency appeared to result from a chronic steatorrhea of undetermined etiology. The clinical and autopsy findings in this case closely resemble those reported by Perkins, Petersen, and Riley.[5]

Interstitial myocarditis associated with potassium deficiency has been observed in patients as well as in experimental animals. Follis and associates[6] studied the development of these lesions in rats. They found that the myocardium first revealed loss of striations, followed by poor staining of the cytoplasm, and finally karyorrhexis and karyolysis. Fatty metamorphosis of the muscle fibers did not occur. Concurrently there was infiltration of the myocardium by neutrophilic polymorphonuclear leukocytes, and large mononuclear cells, and, later, fibrosis. Analysis of the hearts showed a 35 per cent decrease in potassium. Others observed similar chemical and morphologic changes in animals receiving a potassium deficient diet as well as injections of desoxycorticosterone acetate.[7, 8] Myocardial lesions similar to those produced in experimental animals have been encountered in patients with potassium deficiency. Goodof and MacBryde[9] were the first to note focal myocardial necrosis with lymphocytic infiltration in a patient with Addison's disease who had been treated with desoxycorticosterone and showed clinical evidence of potassium deficiency. Myocardial lesions were found by Perkins, Petersen, and Riley[5] in a patient with the sprue syndrome and clinical evidence of severe hypokalemia. The occurrence of potassium deficiency in the sprue syndrome was clinically recognized before morphologic lesions were noted. A report published several years ago described a patient with lymphosarcoma and the clinical evidence of potassium deficiency, but the myocardial and renal changes were not mentioned at autopsy.[10] "Hypokalemic myocarditis" was described by Rodriguez, Wolfe, and Bergstrom[11] in two patients dying in diabetic coma.

The renal lesions in this patient closely resemble those observed in experimental animals with potassium deficiency where fatty metamorphosis occurs followed by necrosis and finally calcification of the epithelium of both proximal and distal convoluted tubules. Fatty metamorphosis of the renal tubular epithelium was distinct in this patient but many of the vacuolated epithelial cells failed to take the fat stain. Perkins and co-workers[5] noted marked vacuolization of the renal tubular epithelium but could not demonstrate the presence of lipid. Darrow and Miller[7] found renal tubular changes, but no myocardial damage, in a few of their animals.

Renal tubular lesions similar to those occurring in patients and animals with potassium deficiency have been described under various names. Williams and MacMahon[12] observed "clear cell nephrosis" in a patient with weak-

ness, weight loss, anorexia, vomiting and hypotension. The electrocardiograms were interpreted as showing left axis deviation and probable myocardial damage. The serum sodium was 125 mEq. per liter and two serum potassium determinations were 2.9 and 3.7 mEq. per liter. The exact manner of the patient's death was not recorded. At autopsy a pancreatic carcinoma "in situ," osteomalacia, coronary artery sclerosis, a small myocardial scar and "clear cell nephrosis" were found. Kulka, Pearson, and Robbins[13] described a "distinctive vacuolar nephropathy" in patients who at autopsy were found to show a variety of intestinal disorders, particularly ulcerative colitis. They mentioned potassium deficiency among the factors possibly related to the renal lesion. Jensen, Baggenstoss, and Bargen[14] observed similar changes in a few patients who died from the complications of chronic ulcerative colitis. It is probable that these renal tubular lesions can be attributed to potassium deficiency, particularly when encountered in patients with long standing, severe, intestinal disorders.

Potassium deficiency should be suspected when weakness and lethargy appear in a patient with electrolyte imbalance. The diagnosis is suggested by the clinical picture, electrocardiograms, and serum potassium determinations. The events which occurred in our patient indicate that potassium deficiency may become a clinical emergency.

Summary

Myocardial and renal lesions of potassium deficiency are described in a patient who died with the sprue syndrome and hypokalemia. Similar renal lesions are described under a variety of names in recent literature. It is suggested that they result from potassium deficiency since they were found in patients who died with disorders commonly associated with electrolyte imbalance.

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CLINICAL PROGRESS

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The Specific Treatment of Syphilitic Aortitis

By R.H. KAMPMEIER, M.D., AND HUGH J. MORGAN, M.D.

HEART DISEASE is the most common cause of death in the United States. Syphilis is the etiologic factor in about 10 per cent of cases and represents one of the types of heart disease which is preventable. Specific, curative remedies are available for the infection. The advent of penicillin therapy in 1943[1] was the most important development in the treatment of syphilis since Erlich's introduction of Salvarsan (606) in 1910.

An understanding of the pathology and natural course of untreated syphilitic cardiovascular disease is essential to any evaluation of treatment, old or new, and will be reviewed in some detail. Following this, the role of specific treatment in the management of syphilitic cardiovascular disease will be discussed.

PATHOLOGY

The basic lesion of cardiovascular syphilis is aortitis. Syphilitic myocarditis and gummas of the myocardium are rare lesions. The frequency of uncomplicated aortitis cannot be accurately determined. Its complications, aneurysm, aortic insufficiency and stenosis of the coronary orifices, are usually easily recognized. They represent the disabling and lethal manifestations of syphilitic cardiovascular disease.

Syphilitic aortitis is a manifestation of acquired syphilis. Congenital syphilis probably never causes aortitis. The few reported cases of congenital cardiovascular disease of syphilitic origin are not convincing.

Syphilitic myocarditis became a controversial topic following Warthin's report in 1931 that spirochetes could be demonstrated in the myocardium of individuals with syphilis and diffuse myocardial degenerative and inflammatory changes. Although a few investigators agree that diffuse syphilitic myocarditis may occur, the vast majority of pathologists relate the myocardial changes in syphilis to the effects of aortic regurgitation, disturbances in the coronary circulation and gummas. Electrocardiographic studies in the acute stages of syphilis reveal that there may be diffuse myocardial involvement as indicated by abnormal T waves and other minor, transient changes. It rarely happens that these changes in the myocardium in early syphilis result in cardiac enlargement and circulatory embarrassment; we have seen only three such cases at Vanderbilt University Hospital in 30 years experience with 2200 acute syphilitic infections.

Gummatous syphilitic involvement of the myocardium is well recognized, approximately 100 cases having been reported. The lesion occurs most often in the myocardium of the left ventricle, particularly at the base of the interventricular septum where it may cause complete heart block. Gumma of the ventricular wall may cause bundle branch block. Myocardial infarction may be simulated by a gumma insofar as electrocardiographic changes are concerned. Indeed, we have seen an occlusive lesion of a coronary vessel produced by an enveloping gumma.

There seems little reason to doubt that the aorta is invaded by spirochetes early in the course of syphilis. The evidence that spirochetemia occurs in acute syphilis is conclusive. Spinal fluid and electrocardiographic changes in early syphilis are indications of focal lesions in the meninges and myocardium, just as the rash, lymphadenopathy and mucous patches indicate focal lesions in skin, lymph nodes and mucous membranes. The aortic wall probably is invaded by *Treponema pallidum* either via the mediastinal lymphatics or directly via the vasa vasorum. Lymphatic vessels and vasa vasorum are especially numerous in the ascending and transverse segments of the aortic arch. This may explain the greater frequency of

From the Department of Medicine of the Vanderbilt University School of Medicine, Nashville, Tenn.

syphilitic disease in these than in the more distal portions. Whether invasion of the aorta is lymphogenous, hematogenous or mixed the result is involvement of the vasa vasorum and lymphatics of the adventitia and media. Lymphocytic and plasma cell infiltration and obliterating endarteritis of the vasa vasorum is associated with necrosis and fragmentation of the elastic tissue of the media. At some point in the course of the acute, generalized infection, many weeks after the seeding of the aorta with *T. pallidum*, widespread destruction of organisms occurs and the disease progresses from the acute to the chronic stage. In the aorta an exquisitely chronic, low grade inflammatory process may go on for years, possibly with periods of exacerbation and remission entirely unrelated to clinical manifestations of disease. This is uncomplicated syphilitic aortitis. In time, perhaps 10, perhaps 30 years after the acute phase of the infection in the aorta occurred, the complications may become manifest: focal weakness of the aorta may lead to aneurysm, general weakness to diffuse dilatation; dilatation of the aortic ring, separation and sagging of the commissures or actual deformity and destruction of the aortic valve leaflets by inflammation may lead to aortic regurgitation; and finally, deformity or narrowing of the ostia of the coronary arteries by aortitis may interfere with the normal delivery of blood from the aorta to the coronary system.

Clinical Considerations

Uncomplicated Aortitis. By definition, uncomplicated aortitis is syphilis of the aorta which produces neither sign nor symptom. The condition cannot be recognized clinically. Its presence is accurately determined only at autopsy. It is the forerunner of the three chief manifestations of cardiovascular syphilis: aortic regurgitation, stenosis of the ostia of the coronary vessels, and aneurysm. Speculations relative to its incidence in individuals with chronic syphilis vary from 20 to 90 per cent! It is the one type of cardiovascular syphilis for which therapy holds great promise.

The literature concerning the frequency of uncomplicated syphilitic aortitis contains no really worthwhile figures. Accurate data can be obtained only from necropsies of individuals with chronic syphilis who die of causes other than aortitis. In 15,000 autopsies at the Philadelphia General Hospital between 1927 and 1937, evidence of cardiovascular syphilis was found in 1042 or 6.9 per cent.[2] There were 192 instances of aneurysm and 216 of aortic insufficiency. The remaining 634 cases were diagnosed simply as aortitis without any statement relative to the presence or absence of angina pectoris or to patency of the coronary artery ostia. Seventy-four per cent of the subjects were males and 68 per cent of these were Negroes. If it is true that the incidence of asymptomatic aortitis is very high in chronic syphilis, it should be related to the fact that only about 10 per cent of patients with chronic syphilis develop lethal syphilitic cardiovascular disease.

The recognition of uncomplicated syphilitic aortitis, in which there are no symptoms referable to the aorta or coronary system and no physical signs of heart or aortic disease, is obviously impossible unless, as some observers believe, diagnostic x-ray changes can be demonstrated. Most students of the subject agree with Kampmeier, Fleming and Glass,[3] and White and Wise,[4] and others that the early diagnosis of cardiovascular syphilis in the absence of aortic regurgitation, aneurysm, or coronary artery narrowing is "practically impossible." Controlled attempts to recognize uncomplicated aortitis by x-ray examinations have met with failure. Blitch, Morgan and Hilstrom[5] were unable to demonstrate aortic dilatation attributable to syphilis in men having "late latent syphilis," a number of whom almost certainly had uncomplicated aortitis. In this study only men with syphilis and in the "aortitis age" were examined. When hypertension, arteriosclerosis, thyrotoxicosis and severe anemia were excluded, these men with chronic syphilis showed no x-ray evidence of aortic dilatation in spite of the fact that uncomplicated aortitis was almost surely present in a considerable number of them.

Since by definition there is absence of involvement of the ostia of the coronary arteries in uncomplicated aortitis, electrocardiographic changes do not occur.

In summary, it must be said that the diagnosis of uncomplicated syphilitic aortitis is entirely inferential. We know that aortitis occurs in a large number of individuals who have chronic syphilis and that in a much smaller number progression occurs in time with the development of one or more of the following complications: aortic dilatation, aneurysm, aortic insufficiency and narrowing of the ostia of the coronary arteries. Since early uncomplicated aortic involvement is frequent and cannot be recognized, and since it is the forerunner of the most common lethal manifestations of syphilitic infection, all chronic syphilis must be regarded as suspect and managed accordingly. Only in this way will asymptomatic aortitis be given treatment and prevented from progressing to fatal complications. In fact, the rationale of treating chronic asymptomatic ("latent") syphilis resides mainly in the fact that it provides prophylactic therapy for cardiovascular syphilis, that is, therapy for uncomplicated aortitis which cannot be recognized.

Aortic Insufficiency. Among the complications of syphilitic aortitis, aortic insufficiency is the most frequent and the most deadly. Yet in relation to the incidence of syphilitic infection, it is not common. The incidence of syphilitic aortic insufficiency in 2,951 cases of late syphilis at Vanderbilt University Hospital was 3 per cent. Cochems and Kemp[6] found the incidence of serious cardiovascular syphilis to be 14 per cent in persons engaged in heavy labor, whereas it was only 8.7 per cent in persons with sedentary occupations; they suggested that syphilitic aortitis has a better chance of remaining uncomplicated when the circulation is not subjected to the effects of heavy manual labor. In the cases of syphilitic aortic insufficiency at Vanderbilt University Hospital, there were 91 instances in Negro males, 37 in Negro females, 27 in white males and 8 in white females.

The diagnosis of syphilitic aortic insufficiency usually is not difficult. Clinical manifestations appear most often during the second or third decade of the infection. Thus the age group involved is from 35 to 50 years in white patients and a somewhat younger age group in Negroes. A relatively small number of cases of aortic insufficiency are discovered in the asymptomatic stage by physical examination. For example, among 163 patients with aortic insufficiency studied at Vanderbilt University Hospital, 25 or 15 per cent were discovered during routine examinations. The early symptoms of aortic insufficiency are exertional dyspnea, orthopnea, paroxysmal dyspnea and cough —all manifestations of left heart failure. The physical signs of aortic insufficiency are quite variable depending upon the degree of incompetency of the valve. Left ventricular enlargement of varying degrees is usually present. The smooth, high pitched, diastolic murmur at the second right intercostal space near the manubrium, which is usually transmitted unchanged along the left sternal border to the apex in anterior cusp defects (Belthaser Foster), and changed to a murmur of rumbling character over the precordium and apex when the posterior aortic cusps are involved (Austin Flint), is characteristic. The signs of aortic regurgitation usually present over the peripheral vessels may be entirely absent if the normal diastolic blood pressure is maintained. If regurgitation is free and there is greatly increased pulse pressure, the classic systolic pistol shot and diastolic Duroziez' murmur over compressed femoral arteries are present together with visible capillary pulsations and abnormally large pulsations over the peripheral vessels. X-ray examination commonly reveals a widened aorta and left ventricular enlargement although early cases may show no abnormalities.

Aneurysm. Another complication of syphilitic aortitis which occurs in the third or fourth decade of infection is aneurysm. The factors of race and sex operate here as in valvular disease.

Incidence figures at necropsy vary greatly. At the Vanderbilt University Hospital only one aneurysm was encountered in 340 consecutive autopsies. Six hundred thirty-three cases of saccular aneurysm were collected from the records of Charity Hospital in New Orleans and Vanderbilt University Hospital by Kampmeier.[7] The ratio of aneurysms in white to Negro patients was 1:3.1. Sixty per cent of the aneurysms were in Negro males, 21 in

white males, 16 in Negro females and 3 in white females.

The diagnosis of aneurysm is usually not difficult. The location of the sac and its relationship to structures which may be compressed determine to a great extent the symptoms and signs. The structures commonly affected are the trachea, major bronchi, lungs, esophagus, pulmonary arteries, vagus and sympathetic nerves, recurrent laryngeal and intercostal nerves, the diaphragm and indirectly the stomach. Pressure erosion of ribs, sternum, and vertebrae by the pulsating tumor occurs not infrequently and rupture may occur externally and into pericardial and pleural cavities, trachea and esophagus. Aneurysm rarely if ever develops after aortic regurgitation has become established in syphilitic aortitis. However, the presence of aneurysm does not protect against the subsequent development of aortic insufficiency. Indeed, the two conditions occur together in about 20 per cent of cases. Expert roentgenologic examination, including fluoroscopy, is essential to diagnosis.

Stenosis of the Coronary Artery Orifices. The third major complication of syphilitic aortitis is interference with the myocardial blood supply resulting from syphilitic involvement of the orifices of the coronary arteries. Ostial stenosis results in precordial pain which must be differentiated from angina pectoris due to other more common causes. Years ago Pincoffs and Love[8] called attention to the involvement of the coronary ostia in the aortic syphilitic process and related this to the occurrence of angina pectoris and death. Stenosis of coronary ostia was present in 20 per cent of the cases of cardiovascular syphilis with aortic regurgitation studied by Kampmeier (Charity Hospital). The right coronary artery is involved more frequently than the left. The normal proximity of the aortic valve leaflets and the ostia of the coronary arteries at the root of the aorta and the occasional congenital upward displacement of the openings (Von Glahn) afford explanations for the frequent association of aortic regurgitation and coronary insufficiency in syphilitic aortitis. The same association may explain in part the rapid downhill course of syphilitic aortic insufficiency in comparison with the more benign course of rheumatic aortic insufficiency.

Since syphilis rarely causes disease of the coronary arteries anywhere except at their orifices, the occurrence of angina pectoris in an individual with syphilis immediately suggests the presence of aortitis and ostial involvement. If aortic regurgitation of moderate degree or aneurysm is present, such a diagnosis can be made with considerable confidence. If marked regurgitation is present, pain may occur without ostial involvement, for it is clear that aortic insufficiency regardless of cause, when associated with a large valvular defect and low diastolic blood pressure, may produce coronary insufficiency in the absence of coronary artery disease. The electrocardiogram is of little value in differentiating such cases from coronary atherosclerosis.

The Course of Cardiovascular Syphilis

Before an evaluation of treatment directed against syphilitic aortitis can be made, it is necessary to be familiar with the natural course of the disease.

Since the diagnosis of uncomplicated aortitis cannot be established with certainty during life, no information is available as to its course. If, as some believe, a large percentage of individuals with chronic syphilis have aortitis then, in a very considerable number, it is uncomplicated and remains of no consequence since not more than 10 per cent develop clinically recognizable cardiovascular syphilis.

Information concerning the prognosis of the complications of aortitis is available.[9] A number of factors appear to be involved in the outcome of untreated aortic insufficiency. The degree of regurgitation is certainly important. Free regurgitation, associated with a low diastolic blood pressure, decreases coronary blood flow and creates a greater burden for the left ventricle than does a slight valvular incompetency with normal pulse pressure. Furthermore, the state of the myocardium, irrespective of syphilis, is an important factor. The myocardium of an old person, experiencing the effects of the aging process, will fail more rapidly in the presence of aortic regurgitation than the myocardium of a younger individual.

Furthermore, coronary atherosclerosis, hypertension, thyrotoxicosis, rheumatic heart disease, anemia or other factors may be present in association with cardiovascular syphilis and exert a very unfavorable influence upon its course. Finally, syphilitic involvement of the ostia of the coronary arteries is commonly present in individuals with syphilitic aortic regurgitation. When the unfavorable effect of aortic regurgitation upon coronary blood flow is augmented by syphilitic narrowing of the orifices of the coronary vessels, or by atheromatous sclerosis of the vessels, the greatly decreased coronary circulation doubtless contributes importantly to an unfavorable course and hastens the development of congestive heart failure.

Studies by Kampmeier and Combs[7] at Vanderbilt University Hospital indicate the great prognostic importance in a given case of the occurrence of myocardial insufficiency. Their data show that within a three year period death occurred twice as frequently in the group of patients who had myocardial insufficiency at the time of admission to hospital as in those who had never experienced decompensation. Of course, this observation is not surprising since congestive heart failure is the cause of death in most cases of syphilitic aortic regurgitation. Obviously this point must be considered in evaluating the effect of specific therapy. Our experience indicates that a life of physical inactivity is conducive to relative longevity in syphilitic aortic insufficiency provided, of course, myocardial insufficiency has not already developed. Once the latter has occurred, physical activity is tolerated poorly regardless of the state of cardiac compensation when the patient is at rest.

The prognosis of aortic aneurysm is almost always gloomy. Except for the rare patient with a saccular aneurysm which has not enlarged enough to involve vital structures, life is measured usually in months after the onset of symptoms. Only 18 of 188 cases of aneurysm studied by Kampmeier lived longer than two years after the onset of symptoms. If these 18 are excluded from consideration, the average duration of life of the remaining 170 patients, after the onset of symptoms, was 6.4 months. A large percentage of these patients had received no antisyphilitic treatment.

We have seen that the outlook for the patient with clinically recognizable syphilitic aortitis is poor. To what extent may it be improved by specific antisyphilitic treatment? Obviously, aortic valvular insufficiency and saccular aneurysm are irreversible processes. Antisyphilitic treatment cannot restore the normal structure of valve or aortic wall. The most that can be hoped for is an arrest of the deforming, destructive process involving the wall of the vessel, the valves and the ostia of the coronary arteries. Conceivably, the latter might become further narrowed by post-treatment congestion and edema of syphilitic inflammatory tissue (Herxheimer reaction) or become wider as the syphilitic inflammatory reaction recedes under treatment. Isolated instances of both sudden death and complete relief from angina pectoris in subjects with chronic syphilis following specific treatment do occur. It is reasonable to assume that syphilitic aortitis which has not become complicated by involvement of the orifices of the coronary artery or of the aortic valves and which has not progressed to focal weakness with aneurysm formation may respond to specific treatment by arrest or actual regression and healing. The infrequent occurrence of syphilitic cardiovascular disease in patients adequately treated early in the course of the infection is strong evidence in favor of this assumption. As has been noted above, it is chiefly to the end of arresting the progress of subclinical aortitis and preventing the development of its lethal complications that "latent" syphilis is treated.

The Results of Treatment before Penicillin

The evaluation of antisyphilitic treatment in persons with complicated aortitis is an extremely difficult task. Since the diagnosis of uncomplicated aortitis cannot be established accurately the effectiveness of treatment is impossible to determine directly. An indirect approach is to observe the post-treatment developments with relation to the complications of aortitis in persons receiving treatment for so-called "latent" syphilis and comparing the

eventual incidence of recognizable cardiovascular syphilis in them with the eventual incidence in untreated "latent" syphilis. This method of evaluation indicates clearly that uncomplicated aortitis can be arrested, that its lethal complications can be prevented. Maynard and Lingg,[10] in a large group of cases, found that cardiovascular syphilis developed five times more frequently in patients who received no antisyphilitic treatment for early latent syphilis than in those who received chemotherapy, and concluded that the incidence of syphilitic heart disease decreased as the amount of antisyphilitic treatment increased. When treatment was delayed until six or more years after the occurrence of the chancre, the incidence of cardiovascular involvement was four times greater than when treatment was completed within three years after the onset of the disease. Additional confirmation is afforded by Howe's[11] observations that the amount of cellular infiltration of the aortic wall in syphilis bears an inverse relationship to the amount of arsphenamine therapy received. Webster and Reader[12] in 1948 confirmed these findings in a study of sections from the aortas of 45 subjects. They found that in only 3 among 19 cases adequately treated was there an active inflammatory process; whereas, active syphilitic inflammation was present in each of 19 untreated subjects. The aortas of five of seven cases in which treatment was inadequate exhibited active inflammation.

These observations together with those of the Clinical Cooperative Group,[13] Kemp and Cochems[14] and others indicate conclusively that adequate treatment of early "latent" syphilis with arsenicals, mercury and bismuth and iodides prevents the subsequent development of cardiovascular syphilis; that established, uncomplicated aortitis is arrested and the complications of aortitis prevented.

Many observers are not convinced that antisyphilitic treatment prolongs life when either syphilitic aortic insufficiency or aneurysm are present. Others believe that specific treatment is conducive to prolongation of life. However this may be, it is true that in the prolonged and sometimes enthusiastic chemotherapy of the arsphenamine era those patients who lived longest commonly received the most treatment!

Padget and Moore[15] considered the results of the specific treatment of aortic aneurysm and aortic insufficiency. They concluded that "properly directed antisyphilitic therapy results in a prolongation of life in two-thirds of the patients with saccular aortic aneurysm or syphilitic aortic insufficiency and that the remaining third come under observation with initially bad prognoses and do not survive sufficiently long for proper therapy to be administered."

Kampmeier and Combs reviewed the records of 163 cases of aortic insufficiency at the Vanderbilt University Hospital. Seventy-five per cent of the subjects were dead. Fifty-five per cent of the deaths occurred within three years of the onset of symptoms. Neither the kind nor the amount of antisyphilitic treatment appeared to alter the course of the disease.

The Modern (Penicillin) Era

It is clear that a scientific evaluation of the results of penicillin in the treatment of latent and chronic, active syphilis of all types must await the passage of time. Penicillin has been used in treatment only since 1944. However, the curative results in acute syphilis and the immediate results in latent and chronic syphilis are so impressive and convincing that the antibiotic has replaced the arsphenamines in therapy.

From a practical point of view the introduction of penicillin in the treatment of syphilis was a development of inestimable importance: it substituted for the relatively toxic arsenicals a relatively nontoxic agent equally potent in treponemicidal action and equally effective in causing resolution of gummatous inflammatory tissue. Intravenous therapy is no longer necessary and the time required for treatment with penicillin can be telescoped into a small fraction of the minimum requirement for the arsenicals. Thus, the technic of the specific treatment of syphilis has become a relatively simple matter. Therapy can be carried out as an office procedure and in a period of a few days. Because of penicillin the number of patients with acute syphilis who receive adequate treatment is being increased enormously. Since this is usually curative treatment it seems certain that the incidence of cardiovascular syphilis, a late result of chronic infection, will diminish greatly.

However bright the outlook for curative treatment of early syphilis by penicillin, it must be categorically stated that no results are available to indicate that the antibiotic will alter significantly the course of events in the established complications of syphilitic aortitis. The factors of importance in prognosis enumerated above apply equally to the cases treated with penicillin and with the arsenicals.

In the pre-penicillin era it was common practice to avoid specific treatment in cardiovascular syphilis if congestive heart failure was present. Patients with cardiac decompensation bore chemotherapy poorly. Therefore, except for the relief of pain in aneurysm and in coronary involvement, arsenicals were avoided under such circumstances. On the other hand, specific treatment was usually employed in all of the complications of aortitis provided the heart was in a state of good compensation. We have seen that uncomplicated aortitis was favorably affected by this treatment. It is probable that on occasions when the complications of aortitis were treated quite early, they became arrested and lethal progression was delayed or prevented. It seems fairly certain that patients with well-developed aneurysms, aortic regurgitation and coronary ostial stenosis were benefited but little if any by arsenotherapy with the usual supplement of bismuth and iodides. It is not likely that penicillin will change this. However, it seems certain that many more patients with cardiovascular syphilis will receive relatively nontoxic, inexpensive penicillin in recommended doses than received arsphenamine.

Recent literature contains reports of the treatment with penicillin of approximately 250 cases of cardiovascular syphilis.[16] In addition to this, 34 cases were treated by us at Vanderbilt University Hospital and Thayer Veterans Administration Hospital. All reports deal with the immediate effects of treatment. Penicillin seems to be tolerated well regardless of either the type of lesion present or the presence or absence of congestive heart failure. Febrile reactions develop within the first 24 hours of treatment in a considerable number of cases but are almost always of short duration and unassociated with untoward developments. A few isolated patients have developed serious complications while under treatment, such as angina pectoris and rupture of aneurysm. It is difficult to interpret these exceptions. They constitute the reason for the practice which is still recommended by us of "preparing" the patient with cardiovascular syphilis for intensive treatment by several weeks of bismuth and iodide therapy or several days of markedly reduced penicillin dosage. Such preparation has been omitted in most clinics in recent years.

The antibiotic may be administered in single daily injections of 600,000 units of procaine penicillin or in six or eight injections daily of aqueous penicillin. In either case therapy should be continued for 8 to 10 days or until 4.8 to 6 million units have been given. Doses two and three times as large have been employed. Another plan of treatment providing slowly absorbed penicillin over a prolonged period is the injection of 600,000 units of penicillin intramuscularly twice a week for six weeks.

Experience indicated that bismuth and iodides probably were beneficial when used with the arsenicals in the treatment of chronic syphilis. It seems reasonable to allow for this possibility and to employ these slowly acting remedies before and after the administration of penicillin. The use of them before penicillin is given in syphilitic cardiovascular disease provides, in addition, the possible advantage of "preparing" the patient for the rapid, powerful action of penicillin.

Summary

Penicillin has made the specific treatment of cardiovascular syphilis easy to give and easy to take and has all but abolished dangerous treatment reactions. Just as the curative therapy of acute syphilis with penicillin is simple and feasible, so is the prophylactic treatment of cardiovascular syphilis in individuals with latent syphilis and uncomplicated syphilitic aortitis simple and feasible. In spite of the fact that the effectiveness of such treatment has not been conclusively established, the prospects seem bright that the incidence of cardiovascular syphilis will decrease sharply in the immediate future.

Cardiovascular syphilis may be treated, with or without preliminary bismuth and iodide "preparation," by the administration of 4.8 to

6 million units of penicillin in a period of 8 to 10 days. Larger doses and longer periods of treatment have been employed. Experience thus far does not indicate that penicillin therapy of established complications of syphilitic aortitis will be any more successful than was therapy of the pre-penicillin era.

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ABSTRACTS

AVITAMINOSIS

Durant, T. M.: Nutritional Factors in Cardiac Disease. Ann. Int. Med. **35:** 397 (Aug.), 1951.

Because patients with congestive heart failure fail to eat adequately, and because liver function is impaired in this disorder, depletion of the protein stores and nonovert vitamin deficiency states are not uncommon; the resulting hypoproteinemia will contribute to the formation of more edema and will lessen the responsiveness to mercurial diuretics. Refractoriness to mercurial diuretics, when due to this cause, can be overcome by the concurrent use of salt-free albumin intravenously. The supplemental parenteral administration of B-vitamin concentrates, when insufficient intake of thiamine is suspected, may eliminate the manifestations of congestive failure when other conventional therapeutic measures have not accomplished the desired result. It is to be anticipated that the development of atherosclerosis and particularly coronary atherosclerosis can be retarded by the ingestion of a diet low in animal and vegetable fats. This reduction in fat intake must be compensated for by the ingestion of a high protein–high carbohydrate diet, but the careful selection of foodstuffs in these categories is essential. Up to now, no other means of affecting the disturbed lipid metabolism of atherosclerotic patients has proved to be effective.

WENDKOS

BLOOD COAGULATION

Eppes, Williford, and Ludovic, Ethel: Demonstration of the "L.E." Cell without Use of Anticoagulants. Blood **6:** 466 (May), 1951.

Since the *Lupus Erythematosus* phenomenon was first demonstrated in heparinized centrifuged bone marrow from patients with systemic lupus erythematosus, it has been shown that it can be caused to develop in cells from normal blood or bone marrow when they are exposed to plasma from these patients. The "blood factor" has been shown to be in the gamma globulin fraction of the plasma proteins. The possibility that the L.E. cells and rosettes are artefacts induced by the anticoagulant or the concentrating technic has not been conclusively eliminated.

In an attempt to determine whether anticoagulants were required for the production of the L.E. phenomenon, concentration technics using defibrinated blood and unmodified blood in silicone-coated tubes were employed. The authors were successful in demonstrating L.E. cells and rosettes in the blood of two patients with systemic lupus erythematosus with both of these technics. They felt that these results indicate that the L.E. cells is not an artefact induced by anticoagulants.

BEIZER

Wellman, W. E. and Allen, E. V.: The Variable Effects of Identical Amounts of Dicumarol on the Prothrombin Values of Different Persons. Proc. Staff Meet., Mayo Clin. **26:** 257 (July), 1951.

Consecutive records were studied of 100 patients receiving 300 mg. of dicumarol the first day and 200 mg. the second day of treatment. They recorded for this study only the prothrombin time on the first day following the second (200 mg.) dose of dicumarol, since after that time it usually was necessary to give more dicumarol or to give vitamin K to produce the desired prothrombin value. The values for prothrombin time of the blood of 100 patients receiving dicumarol were widely divergent. In two in-

stances the prothrombin time was not influenced; in other instances it was prolonged to 80 seconds or more.

In an additional study they administered 300 mg. of dicumarol on the first day; on the second and third days they recorded prothrombin times. The responses, expressed in prothrombin time, were widely divergent, both on the day after the administration of 300 mg. of dicumarol and on the second day after such administration. For example, in two instances the prothrombin time on the second day was unchanged, whereas in two other instances it was prolonged to 80 seconds or more.

This study emphasizes in a tangible way a fact which has been commented on previously: the response of the prothrombin time in different patients to the oral administration of the same amount of dicumarol is widely divergent. The basis for this great divergence in response is obscure. Theoretically, it could be the result of variations in the absorption of dicumarol from the intestinal tract or to some inherent variability of the blood of different patients to the effect of dicumarol.

SIMON

Hartman, R. C., Conley, C. L., and Krevans, J. R.: The Effect of Intravenous Infusion of Thromboplastin on "Heparin Tolerance." J. Clin. Investigation **30**: 948 (Sept.), 1951.

Normal anesthetized dogs were given intravenous infusions of homologous brain thromboplastin. This resulted in a coagulation defect characterized by prolongation of the clotting time, the thrombin clotting time, and the prothrombin time of diluted and undiluted plasma. There was a fall in platelet concentration. There was an increased sensitivity to the anticoagulant action of heparin. Large amounts of thromboplastin resulted in a reduction in plasma fibrinogen.

WAIFE

Pere, S. A. N.: The Effect of Digitalis, Strophanthin, and Novurit on Blood Coagulation. Acta med. Scandinav. **251**: 1, 1951.

An investigation was made to determine whether drugs commonly employed in the treatment of congestive heart failure influence blood coagulation and thereby increase the hazard of thromboembolic complications. The drugs studied were digitalis, K-strophanthin, and Novurit, a mercurial diuretic combined with theophylline. The studies were made on humans and the doses used in vivo were limited to those generally employed therapeutically. The coagulation time, the calcium, prothrombin, and fibrinogen components in the coagulation process, and the fluid balance were all observed carefully. A total of 105 patients with congestive heart failure were observed and compared with a control group of 41 persons without cardiovascular or hemopoietic disease.

Digitalis and strophanthin were found to accelerate the coagulation rate in those patients with congestive heart failure in whom the drugs were effective in relieving the decompensation; in other cases these drugs did not have this effect. The effect of strophanthin was a little more pronounced. These drugs had no effect on the coagulation time of normal subjects. Novurit shortened the coagulation time of all patients with congestive heart failure as well as in the control subjects.

The opinion is expressed that the coagulation effect of these drugs is nonspecific. The effect is believed to be due to their diuretic action. It is felt that when urinary excretion increases, hemoconcentration rises, tissue fluid carrying with it free thromboplastin passes into the circulating blood, and the resulting increased thromboplastin content is responsible for the accelerated coagulation. No significant changes in coagulation time were observed when these drugs were added to blood samples in vitro in therapeutic concentrations and in concentrations 4000 times greater than those usually employed.

ROSENBAUM

CONGENITAL ANOMALIES

Zuckerman, R., Cisneros, F., and Novelo, S.: The Electrocardiogram of Certain Congenital Heart Diseases. Arch. cardiol. de México **21**: 61 (Feb.), 1951.

An electrocardiographic study was made of 30 cases of congenital heart disease with necropsy records. The authors describe a so-called "P congenital" having the following characteristics: high voltage in leads I, II and V_F; predominance of the positive phase in V_1; tendency toward left axis deviation of P. These changes are explained by persistence of right atrial activation and horizontal electric position of the atria.

The morphology of QRS in V_1 in diseases with right ventricular strain is explained as follows: (a) the rsR type is due to right bundle branch block, (b) the high voltage of R with initial slurring is due to hypertrophy of the right ventricle with incomplete bundle branch block, (c) the Rs type is caused by septal hypertrophy without block; if it is notched, there is also incomplete right bundle branch block.

The morphology of left bundle branch block in V_6 is also discussed: (a) rR′ is attributed to left bundle branch block plus left ventricular hypertrophy, (b) RR′ is explained as above, plus septal hypertrophy, (c) Rr′ is explained as due to septal hypertrophy alone.

Negative displacement of ST-T over the right ventricle is described in the tetralogy of Fallot, pulmonic stenosis and patent ductus arteriosus with pulmonic hypertension. Right ventricular ischemia is found in pulmonic stenosis. An "infantile" type of repolarization of the left ventricle in transposi-

tion of the great vessels seems to be due to the inversion of the anatomic structure of the latter.

LUISADA

Boden, E., Bayer, O., and Loogen, F.: The Diagnosis of Congenital Malformations of the Cardiovascular System. IV. The Coarctation of the Aorta. Arch. Kreislaufforsch. **17:** 28 (March), 1951.

The authors discuss the embryology of the aortic system and, in connection with it, the present views on the pathogenesis of coarctation of the aorta. Two principal forms, the juvenile and the adult type, can be distinguished on anatomic, functional and symptomatologic grounds. The clinical diagnosis of the infantile type is difficult, since the time of survival is short and the principal sign, cyanosis restricted to the lower extremities, may be overlooked or masked by association with other congenital malformations. The outstanding signs of the adult type are differences of blood pressure and skin temperature in upper and lower extremities, absent or weak pulsations of the femoral arteries, systolic pulsations of unusual localization and notching of ribs. If Lewis' postulate to examine the femoral pulsations in every case of hypertension is kept in mind, the diagnosis can be made by the general practioner without laboratory aid.

In view of the poor prognosis of untreated coarctation of the aorta, the authors recommend surgical treatment, the optimal time for which is between 8 and 16 years. Results on 3 of the authors' own cases, operated successfully, are presented.

PICK

Myers, G. S., Scannell, J. G., Wyman, S. M., Dimond, E. G., and Hurst, J. W.: Atypical Patent Ductus Arteriosus with Absence of the Usual Aortic-Pulmonary Pressure Gradient and of the Characteristic Murmur. Am. Heart J. **41:** 819 (June), 1951.

The authors present two cases of patent ductus arteriosus in children who did not exhibit the classic machinery murmur. In the first case, a 6 year old boy, there was a grade IV systolic murmur and thrill in the suprasternal notch and in the second and third intercostal spaces both to the right and to the left of the upper sternum. The pulmonary second sound was accentuated and was followed by an early high-pitched grade II decrescendo murmur, heard at the pulmonic area and along the left sternal border. Cardiac catheterization revealed right ventricular and pulmonary hypertension, and a significant increase in oxygen content of blood samples high in the right ventricle and in the pulmonary artery. At operation, a large patent ductus, equal in diameter to the aorta and about 1 cm. in length, was found and successfully ligated. The second case, a 5 year old girl, also had a similarly located systolic thrill and murmur, and an accentuated pulmonic second sound followed by a grade II early high-pitched decrescendo diastolic murmur. Occasionally there was a suggestion of an indistinct machinery murmur underlying the high-pitched early diastolic murmur. During cardiac catheterization, the catheter passed through a ductus into the aorta. There was a gradient in systolic pressure between the aorta and pulmonary artery, 120 and 80 mm. respectively. However, the diastolic pressures were equal, i.e., 50 mm. Biopsy of the lung during ligation of the ductus revealed marked dilatation and mild intimal proliferation of the pulmonary arterioles. The finding of a diastolic pressure in the pulmonary circuit approaching that of the systemic circulation accounts for the absence of a typical continuous murmur, since diastolic flow through the ductus is minimal. The authors note that the reported cases are exceptional in that cardiac catheterization was essential in establishing the diagnosis. Ordinarily, the correct diagnosis is clear following ordinary clinical studies.

HELLERSTEIN

Donzelot, E., Vlad, P., Durand, M., and Metianu, C.: A New Diagnostic Method in Congenital Cardiopathies; A Selective Ether Test in the Course of Cardiac Catheterization. Arch. mal. coeur **44:** 638 (July), 1951.

The authors describe a method to localize intracardiac right to left shunts by injection of a small amount (0.1 to 0.4 cc.) of ether through a cardiac catheter into the pulmonary artery, right ventricle and right auricle. In the presence of an abnormal communication, the ether bypasses the pulmonary circulation at one of the three positions, enters directly into the systemic circulation, producing transient paresthesias or burning sensation of the skin of the face or of the mucous membranes of the pharynx.

The method was used in more than 850 cardiac catheterizations. Side reactions (headache, nausea and vomiting) were rare. However, in 3 children with a massive shunt, the procedure was followed by transient hemiplegia. In the tetralogy and trilogy of Fallot, the ether test proved especially valuable in the distinction of intra-atrial septal defect and anomalous drainage of the pulmonary veins into the right atrium. The test also proved valuable in the diagnosis of a patent ductus arteriosus with reversed flow, and in the diagnosis and localization of veno-arterial communications within the lungs. The method can also be used successfully if there is doubt about the location of the cardiac catheter. Thus with the catheter tip outside the heart shadow, a positive ether test confirms its position in a pulmonary vein.

PICK

Muller, W. H., Jr., and Longmire, W. P., Jr.: Surgical Treatment of Pure Pulmonic Stenosis. Surgery **30:** 275 (Aug.), 1951.

In an attempt to treat pure pulmonic stenosis surgically, the authors devised a special type of valvulotome which could be passed through the right ventricular wall without causing much bleeding. First an incision was made through the full thickness of the wall with a sharp-pointed knife and then the valvulotome was slipped into this opening. When the stenosed orifice was located, pressure was applied to the plunger of the valvulotome, which then enlarged the valve opening to the size of the main pulmonary artery. After this was accomplished, the valvulotome was withdrawn and the opening in the ventricle was closed with interrupted silk sutures.

The operation was performed on three patients and, although no long-range results were available, it was the authors' belief that valvulotomy appeared to be satisfactory treatment for pure pulmonic stenosis.

ABRAMSON

Martin, W. B., and Essex, H. E.: Experimental Production and Closure of Atrial Septal Defects, with Observations on Physiologic effects. Surgery **30:** 283 (Aug.), 1951.

The authors attempted to produce a patent interatrial septal defect in a series of dogs in order to observe the physiologic effects. Several different procedures were utilized. One consisted of passing a long-bladed knife into the right auricular appendage and cutting upward against the interauricular septum, while in another the lateral right atrial wall was opened between two stay sutures and the knife was introduced into the chamber between these. The third involved temporarily interrupting the circulation into the right atrium and incising the atrial wall. Then the atrial septum was picked up with a forceps and a section excised with scissors. The last method consisted of placing a U-shaped row of sutures in the lateral right atrial wall, each suture passing both through the atrial chamber and the opposite portion of the septal wall. The right atrium was then opened in this relatively bloodless area and the septum was incised.

Measurements made of left and right atrial pressures after production of the defect revealed that the mean pressure in the left side exceeded that in the right and that blood was shunted from the left to the right chamber.

ABRAMSON

Burchell, H. B., and Edwards, J. E.: Aortic Sinus Aneurysm with Communications into the Right Ventricle and Associated Ventricular Septal Defect. Proc. Staff Meet., Mayo Clin. **26:** 336 (Aug.), 1951.

The heart of a 36 year old man, who died of heart failure and whose clinical findings had mimicked those of patent ductus arteriosus, was found to have a congenital aortic sinus aneurysm. There were perforations in the aneurysm probably of long duration and the continuous bruit could be attributed to the aortic-right ventricular fistulas. An associated ventricular septal defect was present but it was thought that this probably had played a minor role in the etiology of the heart failure.

SIMON

Effler, D. B., Greer, A. E., and Sifers, E. C.: Anomaly of the Vena Cava Inferior. J.A.M.A. **146:** 1321 (Aug. 4), 1951.

Congenital abnormalities of the vena cava are rarely of clinical significance. However, the authors report a case in which an anomalous vena cava inferior presented itself as a major surgical complication above the diaphragm. In this case the hepatic vein emptied directly into the right auricle and was completely independent of the vena cava inferior. The case is presented because death followed ligation and partial excision of the anomalous vessel. In retrospect, it was felt that this anomaly could have been recognized and surgical problems successfully managed in the course of a right thoracotomy done because of neoplasm presenting in the right main stem bronchus. For many years experienced surgeons have taught that large anomalous vessels in the abdomen must not be ligated and it seems that this teaching should extend to anomalous vessels encountered in the thorax as well.

KITCHELL

Thurnher, B., and Weissel, W.: Ascending Aorta Forming a Contour on the Left Border in Cyanotic Congenital Disease. Cardiologia **18:** 45, 1951.

Four cases of cyanotic congenital disease studied by angiocardiography and catheterization are described. All four cases might have been diagnosed as cases of complete transposition of the large vessels. However, the X-ray in the posteroanterior position revealed a large and long shadow over the upper left margin of the heart which was recognized as belonging to the ascending aorta. Pulmonic stenosis, over-riding aorta, and ventricular septal defect, were found at autopsy.

The unusual abnormality was caused by an ascending aorta which turned to the left earlier than normal so that its shadow was superimposed over that of the descending aorta.

The abnormality is called "incomplete inverse torsion of the truncus." It is considered to be an intermediate stage between complete transposition and total sinus inversus and is explained by the incomplete torsion of the primitive cardiac tube.

LUISADA

CONGESTIVE HEART FAILURE

Ravitch, M. M.: Pectus Excavatum and Heart Failure. Surgery **30:** 178 (July), 1951.

The author briefly reviewed the literature on surgical correction of pectus excavatum in an effort

to point out that evidences of some effect upon the heart by pressure of the displaced sternum are common, and that severe cardiac disability occurs.

The author also reported his experience with a patient who had a marked funnel-breast deformity and developed auricular fibrillation and cardiac failure. The patient was a 28 year old bus driver who had had two episodes of heart failure in the eight months preceding admission. Venous pressures and circulation times were increased. Cardiac catheterization showed marked elevation of right auricular and right ventricular pressure. The cardiac index was 1.4 or 50 per cent of the expected output.

After surgical correction of the deformity the heart shifted medially and anteriorly from its position in the left chest. The patient was asymptomatic, had an increase in exercise tolerance and required neither quinidine nor digitalis. Cardiac catheterization studies done 14 months after operation gave normal pressure figures and a cardiac index of 2.9. The electrocardiogram revealed only slight axis deviation.

The cardiac phenomena associated with pectus excavatum are thought to be on the basis of mechanical pressure directly on the heart, displacement of the heart with possible torsion or angulation of the great vessels and possibly compression of the displaced heart. Pulmonary function is less altered than is cardiac function.

In general, surgery is indicated for correction of the defect for cosmetic reasons as well as for possible alterations in cardiac function. It is felt that the best results are obtained in the youngest patients and when possible, the operation should be undertaken in infancy or childhood.

FROBESE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Wade, E. G., and Jones, A. M.: Cardiac Infarction with Pain Confined to Effort. Brit. Heart. J. **13:** 319 (July), 1951.

The authors re-examined 62 individuals with a history of angina pectoris constantly related to effort, never occurring at rest but relieved by rest, and with no evidence of valvular lesions, of anemia or of syphilis. There were 53 men and 9 women. Seventeen, of whom 15 had enlarged hearts, had electrocardiographic evidence of infarction, 14 had doubtful electrocardiograms and 33 had no electrocardiographic evidence of infarction.

The authors conclude that angina of effort, in the absence of other causes, is due to coronary occlusion with or without subsequent myocardial infarction. The sudden appearance of angina of effort or the sudden intensification of symptoms in established angina should be regarded as an indication of coronary occlusion.

SOLOFF

Gertler, M. M., Driskell, M. M., Bland, E. F., Garn, S. M., Lerman, J., Levine, F. A., Sprague, H. B., and White, P. D.: Clinical Aspects of Coronary Heart Disease. J.A.M.A. **146:** 1291 (Aug. 4), 1951.

A total of 100 patients who had myocardial infarction prior to the age of 40 were studied. One hundred forty-six patients, average age 38, healthy at time of examination, were studied for purpose of comparison. The patients who had had myocardial infarction were selected and had "pure" myocardial infarction, uncomplicated by hypertension, peripheral vascular disease, diseases of the collagen group, diabetes, xanthomatosis, or other recognized metabolic disorders. The group with infarctions consisted of 97 men and 3 women whose average age at the time of the first episode was 38½ years. Thirty-two per cent of the persons in the series were of British ancestry and 27 per cent were Jews. There was a suggestion that myocardial infarction tends to occur more frequently during the winter months. The coronary disease group was characterized by mesomorphic body build and increased levels of serum cholesterol and serum uric acid in contrast to the normal population. The coronary disease victims were shorter and wider with increased anteroposterior chest diameter compared with a control group. There appeared to be a definite relationship between the incidence of coronary episodes and the time of day, with 62 per cent of the initial myocardial infarctions occurring approximately between 7:30 a.m. and 7 p.m. It is thought that activity is not directly related to myocardial infarction although it may accelerate previously existing coronary heart disease into myocardial infarction.

KITCHELL

ELECTROCARDIOGRAPHY

Rodriguez, M. I., and Sodi Pallares, D.: The Electrocardiogram of Aortic Stenosis. Arch. cardiol. de México **21:** 1 (Feb.), 1951.

A comparison is made among the electrocardiograms of 48 cases of aortic stenosis with necropsy findings. All cases of calcific aortic stenosis had either incomplete or complete bundle branch block, 11 of the left and three of the right side. The same was true in five cases of syphilitic stenosis. On the contrary, out of 25 cases of rheumatic stenosis and three of congenital stenosis, only two cases presented left bundle branch block and three, right bundle branch block. In cases having mitral lesions also, disturbances of the cardiac rhythm, especially atrial fibrillation, were frequently present. Atrioventricular block and severe changes of the P wave were not uncommon in the rheumatic cases, but were absent in the others.

LUISADA

Zuckermann, R., Rodriguez, M. I., Monroy, J. R., and Izaza, J.: Electrocardiogram of "Cor Renale." Arch. cardiol. de México **21:** 155 (April), 1951.

An electrocardiographic study of 51 cases of renal diseases is reported. Inflammatory and degenerative diseases of the kidneys are accompanied by low voltage of P and QRS. While the former is explained by electrolytic changes, concentric left ventricular hypertrophy and backward rotation of the apex contribute to the latter. Incomplete left bundle branch block is common in chronic glomerulonephritis and benign nephrosclerosis. As there frequently is evidence of subendocardial lesions, a common factor delaying activation and repolarization of the subendocardial layers seems likely.

Subepicardial ischemia is frequently observed without predilection for the anterior or posterior aspects of the left ventricle.

Premature contractions and paroxysmal tachycardia, frequently observed in arteriosclerosis of the kidney, are explained as the result of hypopotassemia.

The coincidence of low voltage of P and QRS, left ventricular hypertrophy with slight deviation of the axis of QRS, incomplete left bundle branch block with subendocardial lesion, ischemia of any part of the left ventricle, prolongation of QT, and alteration of ST-T of a metabolic type, suggest the existence of a "cor renale." LUISADA

Bartorelli, C., and Folli, G.: Myocardial and Cholinergic Mechanisms of the Vagal Escape. Cuore e circ. **35:** 65 (April), 1951.

The phenomenon of vagal escape was studied electrocardiographically in 32 dogs. The cut vagi were stimulated electrically (frequency 50 per second; duration 0.5 millisecond; 6 volts). Electrocardiographic and arterial pressure tracings were recorded.

Stimulation of the right vagus caused cardiac arrest. This was followed within 30 to 60 seconds by ventricular extrasystoles, then by nodal extrasystoles, and finally by reestablishment of the sinus rhythm.

After left vagal stimulation, the sequence was the following: cardiac arrest; sinus rhythm with complete block and, finally, sinus rhythm with prolonged A-V conduction. The same phenomena were observed when one vagus was left intact.

The cardiac escape following either right or left vagal stimulation was prevented by stimulation of the contralateral vagus.

The different results obtained after right and left vagal stimulation were explained by the different distribution of the left and right vagal fibers to the heart. The mechanism of the vagal "escape" is discussed. The possibility that it is due either to stimulation of sympathetic fibers running with the vagus or to secretion of epinephrine by intracardiac chromaffine tissue is considered. Yet greater importance is given to a diphasic type of action of the acetylcholine which is secreted as a result of vagal stimulation.

LUISADA

Lasser, R. P., Borun, E. R., and Grishman, A.: A Vectorcardiographic Analysis of the RSR Complex of the Unipolar Chest Lead Electrocardiogram. III. Am. Heart J. **41:** 667 (May), 1951.

The authors studied two groups of patients whose precordial leads from positions V_{R7} to V_2 were characterized by an initial position deflection (the R wave) followed by a negative deflection (the S wave), and finally, a late, wide, or slurred positive deflection (the R′ wave). The first group consisted of four patients, ranging in age from 3 to 24 years, with congenital heart disease and right ventricular hypertrophy. The frontal, horizontal and sagittal vectorcardiograms were basically similar to those of two other patients with unequivocal electrocardiographic evidence of right ventricular hypertrophy. The former is believed to be a variant of the latter. The second group with the RSR′ complex consisted of 3 patients, 46, 62, and 71 years of age, with left ventricular hypertrophy, abnormal left axis deviation, and no evidence of right ventricular hypertrophy. The terminal portion of the QRS vector loop departed from the main loop and was directed sharply to the right and anteriorly, forming a terminal "appendage." This form is characteristic of the loop of right bundle branch block as described by Wilson and Johnston. The terminal segment is abnormal, not only its deviation, but also in its irregularity and slow progression. Analysis of QRS loops thus distinguishes between two different conditions which give rise to similar RSR′ complexes.

HELLERSTEIN

Masini, E., and Busnengo, E.: The Atrial Wave of the Electrocardiogram in Arteriosclerotic Heart Disease. Cuore e circ. **35:** 147 (June), 1951.

A study was made of the changes of the P wave in 100 cases of arteriosclerotic heart disease.

A definitely abnormal P wave was observed in 28 cases; the changes were attributed to heart failure. The most typical P-wave changes which were observed were: (a) slightly increased duration (more than 0.12 second); (b) notching and slurring in all leads, diphasic P with broad negative phase in V_1 to V_2 (as seen in mitral defects with left auricular strain); (c) slight and inconstant variations of the voltage and of AP.

These changes can be explained by the dilatation and hypertrophy of the left atrium, due to the left ventricular failure, and by the existence of widespread sclerotic lesions in the atrial walls.

LUISADA

Lasser, R., and Grishman, A.: Vectorcardiograms Obtained in Patients with Right Ventricular Hypertrophy Whose Electrocardiograms Display an Unusual Axis Deviation or Left Axis Deviation. IV. Am. Heart J. **41:** 901 (June), 1951.

Vectorcardiograms were obtained of patients with congenital heart disease whose electrocardiograms

showed an unusual axis deviation or left axis deviation. There were three patients with interatrial septal defect, one with Eisenmenger's complex, three with isolated pulmonary stenosis, and one with tetralogy of Fallot. The diagnosis of right ventricular hypertrophy was established by clinical findings, fluoroscopic examination, angiocardiography, and in three cases, by cardiac catheterization. The position of the ventricles was grossly estimated from the fluoroscopy and angiocardiograms. In the frontal plane projection, the vector loops could be arranged in a graded series, progressing from right axis deviation, through those with negative deflections in all three standard leads to those with frank left axis deviation. The vector loops of the above were inscribed in the right lower quadrant, right upper quadrant, and left upper quadrant respectively, as shown in the frontal plane projection. The horizontal plane projection of the QRS sÊ vector loop presented four patterns. (1) QRS loop in the right anterior quadrant corresponded to the electrocardiographic pattern of tall R waves or RSR complexes from the right side of the chest. (2) QRS loop in right posterior quadrant was associated with the EKG pattern of rS complexes across the entire front of the chest. (3) When the QRS loop was inscribed in the left posterior quadrant, rS complexes were obtained over the right precordium, and tall R waves were found only in leads from the left side of the chest. (4) When the vectorcardiogram was found to lie directly in the sagittal plane of the body, RS complexes were recorded circumferentially about the chest. The authors do not believe that anatomic rotation plays an important role in the production of these bizarre and paradoxical electrocardiograms. They assume that the form and pattern of the ventricular complexes are in some manner determined by the increased thickness of the right ventricular wall or the increased mass and surface area of the right ventricle, altering in unknown fashion the balance of the electromotive forces of accession.

HELLERSTEIN

Glaubach, N.: A New Method in Electrocardiographic Technique for Use in Patients with Somatic Tremor. Am. Heart J. **42:** 142 (July), 1951.

Marked somatic tremors often render the electrocardiogram of little or no value. Although electrocardiograms taken during drug induced sleep are free of somatic tremors, the author believes that a more practical method is desirable. In examining patients with Parkinson's disease, the author noted that there was a minimal amount of tissue movement over the supraglenoid tubercles and over the anterior superior iliac spines, even though there was marked muscle tremor movement of the extremities. Since standard electrodes would not permit ease of application in these areas, electrodes used for electroencephalography were adapted for use. Electrocardiograms so obtained were free of artefacts, and resembled in pattern those derived from the standard positions. The method is practical, can be carried out by one person, eliminates the need for hypnotic drugs, and gives reliable results.

HELLERSTEIN

Burchell, H. B., and Pruitt, R. D.: The Value of the Esophageal Electrocardiogram in the Elucidation of Postinfarction Intraventricular Block. Am. Heart J. **42:** 81 (July), 1951.

The authors present five living cases with electrocardiograms showing posterior wall infarction and delayed intraventricular conduction, which mimics incomplete right bundle branch block in the extremity and left precordial leads but not in the V_1 position. Leads from other positions on the chest were not employed. Esophageal electrocardiograms at ventricular levels showed delayed R waves indicating delayed depolarization of the posterior basal portion of the left ventricle. While the pattern is considered to be characteristically the product of posterior myocardial infarction, slight intraventricular block of the same type was present in a 27 year old man whose heart was clinically normal. In this case, the electrocardiographic aberration was considered to have no clinical significance.

HELLERSTEIN

Taccardi, B.: Measurements of Errors of Vectorcardiography as Function of the Leads Used. Acta cardiol. **6:** 219 (Fasc. 3), 1951.

The author studied variations of the vectorcardiogram under experimental conditions. In order to eliminate distortions of the electrical field by lack of homogeneity of the conducting tissues, an isolated, perfused and beating turtle heart was placed in a circular container filled with Ringer solution and potentials were recorded at various points of its periphery. Vectorcardiograms were then obtained graphically from multiple leads as well as by direct recording with the help of cathode X ray tubes.

It could be shown that under such constant conditions the distribution of the electrical currents in a homogeneous conductor is influenced by a multiplicity of factors and especially by the location of the electrodes. Thus, the orientation of an instantaneous vector may vary by 180 degrees with various positions of the electrode, and the sense of rotation of the vectordiagram may be inversed by a relatively small shift of the location of the electrodes in their relation to the heart. Diametrically opposite bipolar leads, unipolar leads at rectangular axes, or leads arranged according to the conventional Einthoven triangle are the least sensitive to unequal distribution of electromotive forces originating in an electrical source of excentric location.

It is possible that with a tridimensional conductor as represented by the human body the errors inherent in the method may be different and may be related to other axial systems than those defined

under experimental conditions. For the present, clinical vectorcardiography is a method of recording which includes a coefficient of error of unknown magnitude. The latter may influence significantly the correctness of vectorial interpretations.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Taylor, R. D., Page, I. H., and Corcoran, A. C.: A Hormonal Neurogenic Vasopressor Mechanism. Arch. Int. Med. **88:** 1 (July), 1951.

Cross circulation experiments and observations in dogs with spinal cords pithed below the sixth cervical segment and both vagus nerves cut in the neck confirm the hypothesis that a vasopressor substance is liberated into the blood on centripetal vagus stimulation. This substance is shown to be distinct from epinephrine, arterenol (nor epinephrine), renin, angiotonin and pitressin. Its activity is enhanced by large doses of tetraethylammonium chloride and inhibited and ultimately abolished by 1-hydrazinophthalazine (C-5968). This drug also inhibits the pressor action of Serotonin. On appropriate stimulation, the brain can act as an endocrine organ, at which time it releases a pressor substance into the blood. The therapeutic properties of a phthalazine derivative (C-5968) in human beings and in dogs with hypertension of varied origins are consistent with this hypothesis.

BERNSTEIN

Duncan, L. E., Jr., Solomon, D. H., Nichols, M. P., and Rosenberg, E.: The Effect of the Chronic Administration of Adrenal Medullary Hormones to Man on Adrenocortical Function and the Renal Excretion of Electrolytes. J. Clin. Investigation **30:** 908 (Sept.), 1951.

The single administration of adrenaline in man causes increased adrenocortical activity. This study describes the effect of repeated adrenaline administration to four essentially normal subjects. The injections used in this study contained both epinephrine and norepinephrine. After a suitable control period, two subjects received 0.4 mg. of adrenaline in saline subcutaneously every four hours for three days, followed by 1 mg. of adrenaline in peanut oil intramuscularly every four hours for three days; the other two patients received adrenaline in oil for three and six days.

The only evidence of increased adrenocortical activity during adrenaline administration was a decrease in circulating eosinophils and a small change in formaldohydogenic steroid excretion in the first two cases. The other two subjects showed no evidence of altered adrenocortical activity. On this time-dosage schedule, adrenaline is a very weak chronic adrenal stimulus.

There was an increased urinary excretion of sodium, chloride, calcium and uric acid, and diminished excretion of potassium, when adrenaline in oil was administered.

WAIFE

HYPERTENSION

Smith, S. A.: Cerebral States in Hypertension. Proc. Roy. Australasian College of Physicians **6:** 13 (Jan.), 1951.

The pathologic condition underlying the hypertensive encephalopathies and massive hemorrhages within the brain substance is produced by increased intravascular pressure within the smallest arteries, the arterioles, the capillaries and the venules.

The specific hyaline degeneration of the vessel and the condition of necrosing arteritis are the fundamental changes and are due to increased intravascular pressure. Atheroma plays no part, nor does renal disease, although, when present, they may accentuate these changes.

The regulating mechanisms of the circulation operate within wide limits in essential hypertension as they do in the normal subject.

The evidence accumulates that spasm occurs in cerebral vessels and may play an important part in all these phenomena.

Massive intracerebral haemorrhage is the final development in changes of the brain substance, frequently extending over a long time. No unanimity exists as to whether the ultimate source of the bleeding is arterial or venous.

BERNSTEIN

Smirk, F. H., and Alstad, K. S.: Treatment of Arterial Hypertension by Penta- and Hexa-Methonium Salts. Brit. M. J. 1217 (June 2), 1951.

There is a close similarity in the hypotensive effects of penta- and hexamethonium bromides, though formal tests show that hexamethonium bromide is usually slightly stronger in action. Falls in blood pressure following penta- or hexamethonium injections are influenced by posture, being greater as the patient approaches the vertical. On the basis of 150 test doses and treatment of 53 cases, the authors would judge that, apart from some of the cases with impairment of renal function, almost all hypertensives can have their blood pressure controlled by these drugs. Among those with impaired renal function, the four selected for treatment were readily brought under control without deterioration in their renal excretory capacity as judged by nonprotein nitrogen estimations. The hypotensive actions of penta- and hexamethonium salts are enhanced on a salt-poor diet (0.2 Gm. of sodium in 24 hours) to such a degree that dangerous reactions may occur if the effects of this potentiation are not allowed for in determining dosage.

BERNSTEIN

Whitelaw, G. P., and Smithwick, R. H.: Some Secondary Effects of Sympathectomy with Particular

Reference to Disturbance of Sexual Function. New England J. Med. **245:** 121 (July 26), 1951.

The secondary effects of sympathectomy with especial reference to sexual functions was studied by analysis of questionnaires from 161 patients. Procedures included lumbodorsal splanchnicectomy, lumbar sympathectomy, transthoracic sympathectomy and splanchnicectomy, and upper dorsal sympathectomy. Bilateral lumbar sympathectomy led to a change in sexual function in 63 per cent of the patients so treated. Anatomic variations from patient to patient are felt to be responsible for unpredictable responses to the various procedures employed.

Although some female patients reported changes in the menstrual cycle or response to intercourse, the authors feel that these occasional results are probably not due to interference with normal anatomic configuration during operation. Objective disturbances in ejaculation and erection do occur when the bilateral lumbar procedure is extended to include the first lumbar ganglion.

The authors believe that the patient should be apprised of the possibilities before operation and allowed to make the decision.

ROSENBAUM

Wilens, S. L., and Glynn, J.: Hypertensive and Nonhypertensive Periarteritis Nodosa. Arch. Int. Med. **88:** 51 (July), 1951.

A review of 94 cases of periarteritis nodosa disclosed that in 46, or about one-half, hypertension was present on initial examination, and in 11 of these there was a history of hypertension that antedated the onset of periarteritis nodosa. In 17 of the remaining 48 cases hypertension developed secondarily during the course of the disease.

The preponderance of men over women was more pronounced in all hypertensive groups than in the nonhypertensive one. Antecedent hypertensive periarteritis nodosa occurred chiefly in the age period from 30 to 49 years; nonhypertensive and secondarily hypertensive periarteritis nodosa occurred with almost equal frequency at all ages. A higher percentage of the group with nonhypertensive periarteritis nodosa had a history of allergic manifestations. The arterial lesions of periarteritis nodosa in the group with antecedent hypertension tended to be less numerous, to involve smaller vessels and to be less widespread in the various organs than in nonhypertensive group, and were limited chiefly to the abdominal organs and the heart.

Comparison of the lesions in the group of 35 cases in which hypertension was present on initial examination, but in which a history of long-standing hypertension could not be obtained, revealed that the lesions resembled those in the group with antecedent hypertension much more closely than the lesions in the nonhypertensive group. It is suggested, therefore, that in the majority of this group of 35 cases hypertension was present before the onset of periarteritis nodosa.

It is concluded that there is a group of cases of periarteritis nodosa in which preexisting hypertension is an etiologic factor. This group may range from 10 to 50 per cent of all cases of periarteritis. While relative differences exist between this hypertensive group and the nonhypertensive one, there is little reason to believe that the two represent distinct disease entities.

BERNSTEIN

Mackey, W. A., and Shaw, G. B.: Oral Hexamethonium Bromide in Essential Hypertension. Brit. M. J. 4726: 259 (Aug.), 1951.

The authors used hexamethonium bromide (C6), a drug which acts at the ganglionic synapses, in doses of 0.25 to 0.50 Gm. three times daily, in the treatment of essential hypertension in 15 cases. Five of these had a significant lowering of the blood pressure, lasting 6 to 12 months, during the course of this study. Eleven of 12 cases were relieved of headache. The disadvantages of the drug are postural hypotension, dryness of the mouth, constipation, difficulty in ocular accommodation, marked variation in the therapeutic dose from patient to patient, and a narrow range between therapeutic and toxic doses.

BERNSTEIN

Hafkenschiel, J. H., Crumpton, C. W., Shenkin, H. A., Moyer, J. H., Zintel, H. A., Wendel, H., and Jeffers, W. A.: The Effects of Twenty Degree Head-Up Tilt upon the Cerebral Circulation of Patients with Arterial Hypertension before and after Sympathectomy. J. Clin. Investigation **30:** 793 (Aug.), 1951.

The authors studied cerebral circulation in 15 patients who had been subjected to bilateral thoracolumbar sympathectomy, and 18 subjects with essential hypertension. A 20-degree head-up tilt did not change the cerebral blood flow significantly in either group. The cerebral vascular resistance was reduced in both. During the tilt, a significant reduction in "effective" cerebral arterial pressure was noted. Although symptoms of cerebral anoxia were not observed the oxygen uptake of the brain increased in the patients with essential hypertension, but was unchanged in the sympathectomy group, when tilted.

From a study of the oxygen content of the internal jugular vein in the two groups, the authors conclude that the increased cerebral vascular resistance in essential hypertension can be partially relaxed when the arterial pressure is lowered by this slight degree of tilt. Failure of the cerebral vessels to relax completely might be considered as evidence suggesting the presence of significant amounts of circulating pressor substances in patients who have had a sympathectomy.

WAIFE

PATHOLOGIC PHYSIOLOGY

Gordier, D., and Dessaux, G.: Modifications of Glycogen Levels of the Heart in Anoxia, Asphyxia and in Rapid CO_2 Intoxication. Compt. rend. Soc. de biol. **145**: 727 (May), 1951.

It has been shown that lack of oxygen rapidly reduces the glycogen content of the mammalian heart. However, no differentiation has been made between the effect of anoxia, asphyxia and carbon dioxide intoxication. In order to study the glycogen mobilization from the myocardium under these conditions, the authors exposed rats, until death, to controlled atmospheres poor in oxygen.

With complete anoxia, following breathing of pure nitrogen, the rats died within two to three minutes after a phase of severe excitation, and almost 90 per cent of the normal glycogen content disappeared from their heart. In an atmosphere containing equal parts of nitrogen and carbon dioxide, corresponding to asphyctic conditions, the rats developed respiratory arrest, then periodic breathing followed by death in three to five minutes. The glycogen of the myocardium fell to about 40 per cent. Rats, breathing a mixture of 50 per cent carbon dioxide, 20 per cent oxygen and 30 per cent nitrogen, survived for 10 to 20 minutes with slow and superficial respiration, and the glycogen content of the heart was found only slightly reduced. It can be concluded, therefore, that the mobilization of glycogen, induced in the heart by lack of oxygen, is inhibited by carbon dioxide and is probably due to general depression of cellular metabolism by the latter.

PICK

Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J., and Dexter, L.: Factors Regulating Pulmonary "Capillary" Pressure in Mitral Stenosis. IV. Am. Heart J. **41**: 834 (June), 1951.

The authors have analyzed previously reported catheterization data to define the factors which result in recurrent pulmonary edema in rheumatic patients with "tight" mitral stenosis. Observations at rest and during exercise included: calculation of mitral valve area, pulmonary "capillary" pressure (pulmonary artery wedge pressure), pulmonary arteriolar and total pulmonary resistances, cardiac output, diastolic filling period, and mitral valve flow (cc. per diastolic second). Pulmonary edema occurred at rest in all patients whose pulmonary "capillary" pressure rose to 35 mm. of mercury or more, and also in one-half the patients who exercised. Pulmonary "capillary" pressure, considered to be an index of left atrial pressure, was elevated to such high levels in order to maintain blood flow through the mitral valve. Factors which resulted in an increased mitral valve flow rate, thus requiring an elevation of pulmonary "capillary" pressure, were (a) increased cardiac output, and (b) decreased diastolic filling period. The latter was decreased by increases in heart rate and duration of ventricular systole. In patients with mitral stenosis, a normal cardiac output can be delivered only at the expense of a high pulmonary "capillary" pressure. In such patients variations in heart rate, even of a mild degree, and the cardiac output, by leading to increases in valvular flow rate, become the major determinants of pulmonary edema.

HELLERSTEIN

Bateman, J. C.: A Study of Blood Volume and Anemia in Cancer Patients. Blood **6**: 639 (July), 1951.

The study was based on 41 patients with cancer in various stages, and 10 without malignancy. There was no evidence that malignant disease had any specific effect on blood volume. In general, patients with the lowest blood volumes either had severe anemia or had been unable to maintain adequate alimentation for long periods of time. When the total hemoglobin was recalculated on the basis of expected normal blood volume, hemoglobin concentration was reduced when the blood volume was increased, and vice versa. Marked elevations of blood volume were found in patients who had received large doses of stilbestrol; withdrawal of the drug resulted in reversion in one case.

ENSELBERG

Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. McC., and Bradley, S. E.: The Renal and Hepatic Blood Flow, Glomerular Filtration Rate, and Urinary Output of Electrolytes During Cyclopropane, Ether, and Thiopental Anesthesia, Operation, and the Immediate Postoperative Period. Surgery **30**: 240 (July), 1951.

Renal functional disturbances occurring during and after general anesthesia and operation were investigated by the authors in 34 patients. These patients were studied after administration of the preanesthetic medication meperidine, during anesthesia, during operation and after cessation of anesthesia. Electrolyte determinations were made on the plasma and on the urine and the oxygen content of the arterial and venous hepatic blood was measured.

It was found that meperidine and the general anesthetic agents studied had a uniform and nonspecific effect on urine formation and renal hemodynamics. Glomerular filtration and the effective renal plasma flow decreased markedly. Urine flow fell abruptly and the output of urine electrolytes also decreased, but not to the same extent as the urinary flow. Thus the urinary electrolyte concentrations rose slightly. These changes occurred in the absence of a blood pressure drop. Therefore, it was felt that they were due to intrarenal vasoconstriction.

Operation produced no additional change. With termination of anesthesia and operation all values returned to normal.

The authors believe that these vascular readjustments may be due to oversecretion of adrenal cor-

tical hormones and are similar to the homeostatic response to stress seen during shock, chronic anemia, congestive failure, pain, violent exercise, and orthostasis

FROBESE

Taylor, G., and Gerbode, F.: Observations on the Circulatory Effects of Short Duration Positive Pressure Pulmonary Inflation. Surgery **30:** 56 (July), 1951.

The authors believe that positive pressure inflation of the lungs has three chief dangers. They are the production of air embolism, mediastinal emphysema, and circulatory depression.

The fact that air embolism can result from lung inflation pressures above 8 cm. of mercury was confirmed in dogs by these investigators. Also mediastinal emphysema without rupture of the visceral pleura was produced in dogs by pulmonary inflation pressures above 7 cm. of mercury. It was pointed out that these pressures are higher than those used in anesthesia.

The third hazard of circulatory depression was known to occur at lower pressures such as might be used for short periods of time in anesthesia. This circulatory depression is manifested by a fall in the systemic arterial pressure. Various causes for this depression have been proposed. Autonomic reflex pathways have been excluded by most workers. Currently the tamponade factor, in which the venous return to the right heart is impeded, has been held as most important. The authors believe that increased resistance in the pulmonary vascular bed is also a most important factor. To show this, they set up an experiment using dogs which were anesthetized and had the bony chest cage on both sides laid open. The lungs were encased in plastic bags to prevent overdistension. Then positive pressure inflation of the lungs was produced without compression of any of the mediastinal structures. In 15 such preparations there was a substantial fall in the systemic arterial pressure and there was very little rise in the external jugular vein pressure. It was also noted that if only one lung was subjected to a high pressure the circulatory depression did not occur. If, however, a clamp was applied to the pulmonary artery of the undistended lung, thus blocking the free circulatory pathway through it, the usual fall in systemic arterial pressure occurred. Therefore, it was concluded that when all possibility of tamponade had been excluded, positive pressure pulmonary inflation was capable of producing systemic circulatory depression by obstruction of the pulmonary vascular bed.

FROBESE

Jordan, G. L., and De Laney, A. Y: Standard Method for the Production of Pulmonary Edema in the Dog. Arch. Surg. **63:** 191 (Aug.), 1951.

Various methods for the production of pulmonary edema were studied in dogs, in order to obtain a standard procedure which would be successful in a high percentage of the animals and would still produce no physiologic alteration not likely to be found in human beings with this condition.

Rapid blood transfusion in normal dogs and after pneumonectomy, hypoxia and rapid saline infusions, and inspiratory resistance and rapid saline infusions produced pulmonary edema in a small percentage of animals subjected to each procedure. Only when a combination of hypoxia, inspiratory resistance and rapid infusions of saline was used, however, was the condition produced in almost all cases.

ABRAMSON

Scott, H. W., Jr., and Bahnson, H. T.: Evidence for a Renal Factor in the Hypertension of Experimental Coarctation of the Aorta. Surgery **30:** 206 (July), 1951.

The authors review two opposing views concerning the cause of hypertension occurring in coarctation of the aorta which have been prevalent. The first is that the hypertension resulted from resistance to the blood flow caused by the aortic stricture and the collateral vessels. More recently it has been proposed that there is a generalized increase in vascular resistance due to changes in renal hemodynamics.

The authors produced an experimental coarctation in dogs by anastomosing the left subclavian artery to the aorta as far distal as it would reach, and then dividing the aorta between the origin of the subclavian above and the anastomosis of the subclavian below. This created a reduction in the cross-sectional area of the aortic isthmus of 66 to 94 per cent. This procedure was survived by 23 animals.

After operation there was an immediate fall in the mean femoral pressure followed by a slow rise to normal. There was a gradually progressive rise in the mean carotid pressure which reached a hypertensive level in five to seven weeks. This did not support the mechanical hypothesis, as these pressure changes did not take place at once.

In eight of the animals with experimental coarctation and hypertension one kidney was transplanted into the neck and the other kidney was removed. Four of these animals survived for study. In all four of these dogs the mean carotid pressures fell to normal or below normal levels observed prior to the production of the coarctation. This drop occurred by the third week after renal transplantation.

In an additional five dogs with experimental coarctation and hypertension, one kidney was transplanted in the groin below the aortic stricture and the other kidney was resected. Only one of these animals survived and there was no lowering of its mean carotid pressure.

These investigators suggest that the hypertension of experimental coarctation is produced through a

renal mechanism rather than by increased resistance caused by the aortic stricture and the collateral vessels.

FROBESE

Weinberg, S. L., and Schoenwetter, A. H.: Auricular Flutter and Indirect Cardiac Trauma. Arch. Int. Med. **88**: 257 (Aug), 1951.

A case is presented of transient auricular flutter following nonpenetrating injury to the chest in a 59 year old man known to have hypertension, auricular premature systoles, and P wave abnormalities in the electrocardiogram. As far as can be determined, this represents the sixth instance reported of auricular flutter following such injury. While the etiologic basis of the flutter in this instance remains obscure, the possibility of injury to an already damaged auricle is considered and seems to be a reasonable explanation. The case is shown to illustrate a common type of nonpenetrating chest injury, in which the factors of emotion, exertion and actual anatomic damage may lead to abnormal cardiac rhythm, particularly in persons with previously existing cardiac changes.

Approximately 18 months following injury the patient had spontaneous auricular fibrillation with periods of auricular flutter. Mild congestive heart failure appeared for the first time. The relation of this recent episode to the chest trauma, or to previously existing cardiac lesions, remains obscure.

BERNSTEIN

Prinzmetal, M., Oblath, R., Corday, E., Brill, I. C., Kruger, H. E., Smith, L. A., Fields, J., Kennamer, R., and Osborne, J. A.: Auricular Fibrillation. J. A. M. A. **146**: 1275 (Aug. 4), 1951.

Studies made by the authors, including direct and extensive observation of the fibrillating auricle in man and experimental animal, indicate that all the previous theories concerning the mechanism of auricular fibrillation are invalid. They find that mechanical and electrical activity in clinical auricular fibrillation is similar to that observed in experimentally produced arrhythmia. Motion of the fibrillating auricle was directly visualized in high speed cinematographs of the exposed heart recorded in human subjects during surgical removal of auricular appendix and in experimental animals during bouts of fibrillation produced by local application of aconitine or electrical stimulation. In both, cinematographs revealed the presence of chaotic, continuous, rapid, mechanical activity of the type never before described. No evidence of circus movement, macroscopic or microscopic, is visible in cinematographs of the fibrillating auricle of man or experimental animal. Cathode ray oscillograms of auricular fibrillation recorded from direct auricular leads in experimental animals and from esophageal leads in man correspond to the microscopic and macroscopic mechanical events visualized in the cinematographs. Cinematographic and oscillographic study of the onset of auricular fibrillation indicates the arrhythmia represents an advanced degree of conduction failure which occurs when the rate of discharge from the ectopic focus is too rapid to permit adequate conduction recovery in the auricle between successive contraction and excitation processes. Any agent that reduces the degree of conduction failure either by slowing the rate of discharge from the ectopic focus or by improving auricular conductivity tends to terminate auricular fibrillation. The antifibrillary action of quinidine is related to the ability of the drug to slow the rate of discharge from an ectopic focus on the auricles and consequently to mitigate the conduction failure induced by rapid auricular rate. Digitalis generally increases the rate of discharge from the rapidly discharging focus in the fibrillating auricle and tends to perpetuate auricular fibrillation.

KITCHELL

PHARMACOLOGY

Reid, G.: The Vasoconstrictor Activity of Serum. Proc. Roy. Australasian College Physicians **6**: 68 (Jan.), 1951.

Platelets adhering to abnormal vessel walls may liberate a vasoconstrictor substance in sufficient quantity either to cause local spasm of the vessel or to be carried into the peripheral field of distribution, there to exert its effect. These considerations may have a bearing on the transient vascular accidents sometimes observed in patients with vascular disease. One may suggest that this substance may be implicated when clinical coronary occlusion is unassociated at autopsy with an actual thrombosis.

There exists in the body, and in the lungs in particular, a mechanism for the destruction of the vasoconstrictor substance in the blood stream. The responsible enzyme is a monoamine oxidase.

The nature of the substance active in vasoconstriction indicates that the crystalline preparation is a tryptamine derivative. The evidence indicates that the active substance is 5-hydroxytryptamine, but this view may be modified. The substance has not been synthesized.

It is interesting to consider the possibility that another, yet unknown, pharmacologically active amine may play a part in physiologic and pathologic processes.

BERNSTEIN

Mosey, L., Maison, G. L., and Stutzman, J. W.: Cardiac Effects of a Hypotensive Veratrum Derivative in Dogs Premedicated with Digitalis or Quinidine. Proc. Soc. Exper. Biol. & Med. **76**: 486 (March), 1951.

Veriloid, a hypotensive derivative of veratrum viride, was administered to unanesthetized dogs, and to unanesthetized dogs premedicated with toxic

doses of digitalis preparations, and to others premedicated with toxic doses of quinidine hydrochloride. The degree of cardiac slowing from the Veriloid was a function of the pre-existing cardiac rate. The rate reduction produced by digitalis was found to be independent of the original rate. The dogs that received digitalis and Veriloid showed a profound bradycardia, and this action appeared to be mediated by increased vagal tone, since the slowing was abolished by atropine. Disturbances in rhythm due to digitalis were exaggerated by veratrum. A rise in Q-T/R-R ratio above that to be expected by changing cardiac rate was associated with the administration of quinidine hydrochloride. In normal animals, and in those which received digitalis, Veriloid or both, the ratio was found to vary as a straight line function of the existing heart rate. Neither quinidine alone at 15 or 25 mg. per kilogram nor quinidine and veratrum produced any appreciable incidence of arrhythmias. Cardiac slowing was observed with the 15 mg. per kilogram dose of quinidine but not after the 25 mg. per kilogram dose.

MINTZ

Burn, J. H.: Antidiuretic Effect of Nicotine and Its Implications. Brit. M. J. 4725: 199 (July), 1951.

Smoking, or the intravenous injection of nicotine, can be shown to inhibit a diuresis caused by drinking water in man. The inhibition is due to the release of the antidiuretic hormone from the posterior lobe of the pituitary, because this hormone is found in the urine after smoking. This hormone is believed to be the same as vasopressin, which constricts blood vessels, including the coronary vessels.

Nicotine produces a coronary constriction in the dog. Ordinary smoking of one or two cigarettes liberates in man from 3 to 190 milliunits. Concentrations equal to 100 milliunits in 5 liters of blood are sufficient to cause coronary constriction in the coronary vessels of the dog, and may therefore have the same effect in man.

BERNSTEIN

Braun, K., and Freyd, C. H.: The Effect of Priscol on the Peripheral Venous Pressure. Brit. Heart J. 13: 294 (July), 1951.

The response of the venous pressure to Priscoline was studied in 22 individuals, five of whom were normal, four who had hypertension without failure, three who had hypertension and failure, four with valvular disease and failure, and four with cor pulmonale and failure.

There was a decrease in venous pressure in all except three normal subjects. The greatest fall occurred in those with cor pulmonale. In three who were subsequently digitalized, the magnitude of the fall was diminished. The drop in venous pressure was accompanied in all cases by a fall in arterial pressure.

These results are interpreted as due to the sympathicolytic action of priscal on venous tone.

SOLOFF

Joseph, S. I., Helrich, M., Kayden, H. J., Orkin, L. R., and Rovenstine, E. A.: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrhythmias Occurring during Thoracic Surgery. Surg., Gynec. & Obst. **93**: 75 (July), 1951.

The authors investigated the usefulness of Pronestyl as a prophylactic agent and as treatment for arrhythmias in 22 patients undergoing surgery during cyclopropane anesthesia. The drug was given orally, in doses of 1.0 to 2.0 Gm., one to two hours prior to induction of anesthesia. During thoracotomy an additional 1.0 Gm. was administered intravenously.

When administered prophylactically, Pronestyl reduced the incidence of all types of arrhythmias, especially of ventricular origin, for extended periods of time. The drug was found to be uniformly useful in ventricular arrhythmias. Oral and intravenous administration provided clinically effective plasma levels for a prolonged period of time. The importance of adequate dosage was emphasized.

ABRAMSON

Joseph, S. I., Helrick, M., Kayden, H. J., Orkin, L. R., and Rovenstine, E. A.: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrhythmias Occurring during Thoracic Surgery. Surg. Gynec. & Obst. **93**: 75 (July), 1951.

In an experimental group of 22 patients in whom cyclopropane anesthesia was employed, procaine amide was administered orally prior to induction of anesthesia and intravenously during operation. In the large majority of patients the surgery was intrathoracic in nature. A control series of 25 patients was studied for comparison. Analysis of data indicated that, prophylactically, procaine amide significantly reduced the incidence of all types of arrhythmias, and especially of ventricular tachycardia. Ventricular arrhythmias observed were regularly reverted to normal sinus rhythm by the therapeutic administration of the drug. Clinically effective plasma levels of procaine amide were found for extended periods of time after both oral and intravenous administration. An analysis of the factors responsible for the precipitation of ventricular arrhythmias during cyclopropane anesthesia suggested that the major role is played by inadequate ventilation.

SAGALL

Ureles, A. L., and Kalmassahn, R. B.: Oral Administration of Cortisone in a Case of Erythema Nodosum. New England J. Med. **245**: 139 (July 26), 1951.

A male aged 28 years, suffering from severe, persistent erythema nodosum, was given cortisone orally

after salicylates, tripelennamine hydrochloride, and procaine penicillin had all failed to alter the clinical picture. Relief of pain, rapid fading of the skin lesions, and fall in temperature occurred within 12 hours after the initial dose of cortisone. The initial dose was 100 mg. twice daily for five days. When on a maintenance dose of 25 mg. twice daily a recrudescence of erythema nodosum occurred with remission when the dose was increased. The drug was discontinued after treatment for one month and the patient had remained asymptomatic and afebrile for two months at the time this report was made.

ROSENBAUM

Nosik, W. A.: Stellate Ganglion Block in Cerebrovascular Accidents. Ann. Int. Med. **35**: 409 (Aug.), 1951.

Repeated infiltrations with procaine in the immediate vicinity of the stellate ganglion can easily and safely block this structure if the simple technic advocated by de Sousa Pereira is followed. This procedure, performed on the same side as the cerebral lesion, has proved to be of benefit in the cases of cerebral embolism, thrombosis, and hemorrhage which the author has treated. The benefits are difficult to measure, but it is believed that this procedure may result in a decrease of neurologic residua and a lessening in the degree of permanent disability. The rationale for the procedure is the elimination of vasospasm of the arterioles and venules supplying the zone of neurones surrounding the affected area, thus promoting the development of collateral circulation and lessening local edema.

WENDKOS

Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisal, E. C.: "Water Diuresis" Produced during Recumbency by the Intravenous Infusion of Isotonic Saline Solution. J. Clin. Investigation **30**: 862 (Aug.), 1951.

The intravenous infusion of 3 liters of isotonic saline in 3 normal individuals led to a "water diuresis." The excretion of water, in excess of solutes, is characteristic of the ingestion of water, exposure to cold, and damage to the supraopticohypophyseal system, and may be inhibited by the administration of Pitressin. The authors observed that this isotonic expansion of extracellular fluid volume was ineffective in the sitting subject but did produce a water diuresis during recumbency.

Since the equal expansion of extracellular fluid volume in the sitting subject does not significantly diminish antidiuretic activity, the authors suggest that the distribution as well as the magnitude of the expanded extracellular volume is of importance in water diuresis.

WAIFE

Irvin, C. W., Jr., and Cutts, F. B.: Ventricular Tachycardia. J. A. M. A. **146**: 1282 (Aug. 4), 1951.

The authors report a case of ventricular tachycardia occurring in a 35 year old man who had had an acute anteroseptal myocardial infarction 3 days previously. This individual had severe reactions with both oral and intravenous quinidine. On the sixth day, Pronestyl (procaine amide hydrochloride) 500 mg. was given every fourth hour. In 12 hours the electrocardiogram showed normal sinus rhythm. On the thirty-first day the patient was discharged. One week after discharge he was readmitted with a second bout of ventricular tachycardia and this was again controlled by oral administration of procaine amide hydrochloride. Following discharge he was instructed to take 1 Gm. of Pronestyl on arising and at bedtime and 0.5 Gm. every three hours during the day. A month and a half later he died suddenly after a bout of palpitation which his family said was similar to previous attacks. Although procaine amide hydrochloride was successful in terminating at least two attacks of ventricular tachycardia, it did not prevent, in tolerated doses, what was apparently a fatal arrhythmia.

KITCHELL

Dönhardt, A.: Investigations on the Effect of Glycosides on the Electrocardiogram. I. Digitalization of the Healthy Normal Heart. Ztschr. f. Kreislaufforsch. **40**: 528 (Sept.), 1951.

The author studied alterations of the electrocardiogram produced in 170 normal persons by the usual therapeutic dose of various digitalis preparations. The earliest change was shortening of the Q-T distance followed, with higher dosage, by deformation of the S-T segment and T wave. Prolongation of the P-R interval to abnormal values was seen infrequently and only when the initial P-R measured more than 0.14 second. The time of restitution of the electrocardiographic changes was found to depend on the tendency of the particular preparation to cumulation. Thus alterations following purpurea glycosides persisted longer than those seen following Cedilanid. S-T deviations and alterations of the contour of the T wave persisted longer than the shortening of Q-T. The degree of electrocardiographic changes was not correlated with the dose of the preparation used and the results varied in repeated experiments with the same person. The author concludes that the electrocardiogram is not a suitable method for determination of the potency of a digitalis preparation.

PICK

PHYSICAL SIGNS

Calò, A. Tripartition of the Atrial Sounds in a Case of Complete A-V Block. Cuore e circ. **35**: 168 (June), 1951.

A case of complete A-V block is presented and the unusual phonocardiogram is discussed. The atrial sounds of the atrial contraction corresponding to the

blocked impulses, were unusually long, lasting 0.34 second.

For each atrial contraction, there were three groups of vibrations, similar to those more commonly seen in endocardiac or esophageal phonocardiogram. The first group of small vibrations, starting 0.04 second after the beginning of the P wave, is explained as due to the atrial contraction. The second group of more ample vibrations, starting 0.12 second after the P wave, and coincident with the peak of the A wave of the phlebogram, is attributed to the distension of the ventricular wall by the atrial wave and to a rebound of the valvular leaflets. The third group of small vibrations, starting 0.15 to 0.27 second after the P wave, and coincident with the descending slope of the A wave, is explained as due to the elastic retraction of the ventricular wall, previously distended.

LUISADA

Besterman, E. M. M.: The Use of Phenylephrine to Aid Ausculation of Early Rheumatic Diastolic Murmurs. Brit. M. J. 4725: 205 (July), 1951.

Phenylephrine, a sympathomimetic drug with a noradrenaline-like action, has been given to 64 patients, of whom 35 had rheumatic carditis. Transient elevation of the blood pressure and reflex bradycardia occurred in like degree in both nonrheumatic and rheumatic cases with and without carditis.

Transient aortic and mitral diastolic murmurs were induced by means of phenylephrine in many cases of rheumatic carditis, but never in nonrheumatic patients or in cases of rheumatic fever without carditis. Aortic diastolic murmurs so induced are attributed chiefly to an increased load from transient hypertension straining a damaged aortic valve. Mitral diastolic murmurs are mainly attributed to an increased mitral blood flow associated with an augmented stroke volume resulting from reflex bradycardia. However, other factors appear to be implicated. Such murmurs offer clear evidence of valve damage and may be of considerable diagnostic aid.

BERNSTEIN

Caló, A.: The Elastic Reaction of the Ventricles and the Fifth Heart Sound. Cardiologia **18**: 112, 1915.

The author had previously described a graphic phenomenon consisting of an additional low-pitched sound after the third heart sound. To this, he gave the name of "fifth sound."

Having found this sound in seven new cases, the author tries to explain the mechanism of its production. This sound appears from 0.08 to 0.16 second after the third sound.

Following rapid ventricular filling, which is revealed by the third sound, an elastic reaction of the ventricular wall is postulated. This would set up vibrations in the myocardium and possibly in the cardiac valves.

LUISADA

PHYSIOLOGY

Franck, C., and Grandpierre, R.: The Effects of Faradic Stimulation of the Phrenic Nerve upon Respiration and Circulation. Compt. rend. Soc. de Biol. **145**: 693 (May), 1951.

Faradic stimulation of an intact root of the phrenic nerve in the anesthetized dog produces tetanic contraction of the homolateral diaphragm with apnea; followed shortly afterward by increased respiratory movements of the diaphragm of the opposite side. These changes in respiration are frequently, but not always, associated with elevation of the blood pressure. The same effect on respiration, together with hypotension, is obtained after cutting the phrenic nerve and electrical stimulation of the peripheral stump. Faradization of the central end of the nerve results in hyperventilation and moderate hypertension. All of these changes in respiration and circulation can also be obtained if the vagus nerves are sectioned before stimulation of the phrenic nerve.

The experiments confirm the existence of centripetal fibers in the phrenic nerve, transmitting, independent from the vagus nerves, reflex impulses to the respiratory and vasomotor centers. Faradization of the intact phrenic nerve thus produces both centrifugal motor and centripetal sensory impulses, the interplay of which leads to various adjustments of blood pressure and respiration.

PICK

Kuntz, A.: Afferent Innervation of Peripheral Blood Vessels through Sympathetic Trunks: Its Clinical Implications. South. M. J. **44**: 673 (Aug.), 1951.

The author investigated the problem of the abundance of afferent spinal nerve fibers which enter the extremities through the communicating rami and the sympathetic trunk. The study was performed on cats and human subjects.

Using the evidence obtained from histologic studies of nerves after division of various portions of the thoracic and lumbar spinal nerves, and of the sympathetic trunk in cats, the author concluded that some afferent spinal nerve fibers reach the extremities through the sympathetic trunk. Physiologic data also appeared to support the contention that a number of the fibers in question conduct impulses of pain, these being distributed chiefly in relation to blood vessels rather than to the skin and muscles of the extremity. It was the author's opinion that interruption of the afferent fibers associated with sympathetic nerves eliminates one of the important afferent pathways through which pain is mediated and that this mechanism is in part responsible for the improvement brought about by sympathectomy. The other factor in the alleviation of pain is sympathetic denervation of the blood vessel itself, particularly if vascular hypertonus or vasospasm is originally the cause of the symptom.

ABRAMSON

Gerst, G. R., Grossman, J., and Kantrowitz, A.: Oxygenation of Blood by Isolated Lung. Science **114**: 258 (Sept. 7), 1951.

An isolated heart-lung preparation of a cat was used to study the oxygenation of the blood through a lung attached to a source of oxygen under intermittent positive pressure. Without special care as to sterility or temperature, it was found that blood was completely oxygenated during a single passage through the isolated lung.

Other factors remain to be determined. These include the interval following the removal of the lungs during which function is retained, the maximal blood flow permitting efficient oxygenation, and the maximum duration of function under mechanical propulsion.

WAIFE

Bierman, H. R., Kelly, K. H., King, F. W., and Petrakis, N. L.: The Pulmonary Circulation as a Source of Leucocytes and Platelets in Man. Science **114**: 276 (Sept. 14), 1951.

Following the administration of intravenous epinephrine, blood was sampled from intravascular catheters placed in the right ventricle and a large systemic artery. It was observed that an increase in the number of leukocytes and platelets in the arterial samples exceeded that found in the venous blood by at least one or two circulation times. The arterial-venous platelet difference was more marked and sustained than the leukocyte difference. These experiments illustrate that in some patients the lung may be stimulated to deliver platelets and leukocytes promptly into the circulation.

WAIFE

Lagerlöf, H., Eliasch, H., Werkö, L., and Berglund, E.: Orthostatic Changes of the Pulmonary and Peripheral Circulation in Man. Scandinav. J. Clin. & Lab. Investigation **3**: 85, 1951.

In this study direct measurements are made of the pulmonary arterial and venous pressures, pulmonary resistance and pulmonary blood volume in the horizontal and 60 degree posture in two patients, one normal and one hypertensive. In the upright position the hydrostatic mean pressure in the carotid sinus and aortic arch pressoreceptors diminishes. The pulse rate and the peripheral vsacular resistance increase within a few seconds and carotid sinus pressure returns to its previous level. Simultaneously, pulmonary and systemic venous pressures decrease due to dilation and pooling of blood in veins and capillaries of lower parts of the body. Decrease in the right atrial and pulmonary capillary venous pressure pulses indicates that the fall in venous pressures is greater than that due to descent of the diaphragm. Diastolic filling of both ventricles decreases with the lower venous pressures. The stroke volume of the right ventricle decreases first, followed by the left. For a short period the left ventricle ejects more blood than the right, thereby decreasing pulmonary blood volume. Conditions are reversed in tilting from the 60 degree position to horizontal. The pulmonary vascular bed acts as a blood depot.

OPPENHEIMER

SURGERY IN HEART AND VASCULAR SYSTEM

Wright, D.: Endarteriectomy for Chronic Endarteritis. Brit. M. J. 4723: 95 (July), 1951.

A 40 year old white male, with a localized block of the femoral artery at the lower end of Hunter's canal secondary to a traumatic thrombus incurred six years previously, was subjected to an endarteriectomy. One month after operation the posterior tibial pulse was easily felt and the patient could walk without the slightest suggestion of a claudication pain.

Although it is too early to claim a permanent cure in this case, the author feels that the results of the operation are most encouraging and that the method is worthy of further trial.

BERNSTEIN

Sako, Y.: Prevention of Dilatation in Autogenous Venous and Pericardial Grafts in the Thoracic Aorta. Surgery **30**: 148 (July), 1951.

Several investigators have found that pericardial tube or vein grafts placed in the thoracic aorta undergo an aneurysmal dilatation. Therefore, interest was centered on finding a method capable of avoiding this complication.

Forty pericardial tube grafts were constructed in dogs. These were placed distal to the ductus arteriosus and were 2 to 3 cm. in length. In the 24 surviving animals dilatation of the insert occurred. Endothelialization of the graft was marked after seven days. In grafts with marked dilatation, this endothelialization was irregular and there was a tendency to thrombus formation. Deposition of cholesterol was also noted.

Pericardial tube grafts buttressed with fascia taken from the thigh were used to bridge aortic defects in 25 animals. The 16 dogs which survived have been followed by serial aortograms; the longest follow-up has been 18 months. No dilatation occurred in this group. Endothelialization proceeded in a more uniform pattern and cholesterol deposition did not occur.

Similar studies, in which segments of the vena cava were buttressed with fascia lata and placed across aortic defects, were made. Segments up to 4.5 cm. in length were used in 10 dogs and no dilatation occurred.

Attempts to support vein grafts with split thickness of skin or dermis were unsuccessful because of infection about the grafts. It was very difficult to rid the skin crypts of bacteria.

Autogenous vein and pericardial tube grafts to

the thoracic aorta have a high rate of survival. The use of fascial support about these grafts may be warranted as it appears that dilatation can be prevented. Also the endothetial lining produced is more uniform and cholesterol deposition does not occur.

FROBESE

Muller, W. H., and Longmire, W. P., Jr.: The Surgical Treatment of Cardiac Valvular Stenosis. Surgery **30**: 29 (July), 1951.

Pure pulmonic stenosis is often associated with an auricular septal defect. It differs from the tetraology of Fallot in that there is an intact ventricular septum. Cyanosis is present when a patent foramen ovale exists and its degree depends upon the size of the opening. Systemic artery–pulmonary artery anastomosis is contraindicated in pure pulmonic stenosis because it produces right heart failure. Instead a direct attack on the stenotic valve is necessary.

The authors describe their operative technic and the instruments they have devised for incising and dilating stenotic pulmonic valves through the right ventricle. They have performed pulmonic valvulotomy on five patients with no deaths.

Cyanosis had been present in two of these cases. Exercise tolerance was markedly diminished in two patients. All had a marked thrill in the main pulmonary artery and all had a post stenotic dilatation of the pulmonary artery. It was felt that all the cases were improved after valvulotomy. The thrill persisted in each case, but it was less intense. Catheterization studies done in one case three months after valvulotomy showed a marked lowering of the right ventricular pressure. Pulmonic insufficiency resulting from the valvulotomy has been well tolerated.

The authors have also operated on 14 patients with mitral stenosis using an operative technic similar to that described by Bailey. Three deaths resulted. Nine cases had advanced pulmonary hypertension with pulmonary edema and hemoptyses. Six cases had peripheral emboli. Five cases had had auricular fibrillation.

The survivors improved subjectively after valvulotomy. Systolic murmurs have been present in eight patients after the operation, but a diastolic murmur has been absent in all but one case.

It should be emphasized that the best results occur in young patients with only increasing exertional dyspnea and easy fatigability rather than those with advanced pulmonary hypertension. However, the latter group should be included and given the opportunity of relief. Preoperative catheterization studies should be done in selecting cases for operation. Contraindications to operation are severe aortic insufficiency, acute rheumatic fever, subacute bacterial endocarditis, and recent emboli.

FROBESE

Lynn, R. B., and Shackman, R.: The Peripheral Circulation during General Anesthesia and Surgery. Brit. M. J. 4727: 333 (Aug.), 1951.

It has been confirmed by venous occlusion plethysmography that increased limb flows are maintained during the whole period of relatively minor operations and during the earlier phases of more prolonged and severe operations. During the later phases of more prolonged and severe operations the limb flows decline in most cases and become equal to or somewhat less than the preanesthetic resting levels. It is concluded that the increase in peripheral blood flow noted during anesthesia results from active vasodilatation in the limb vessels. The decrease in limb flow from the peak level, noted in the later stages of the more severe operations is due to a relative vasoconstriction in the peripheral circulation. The rapid onset of vasodilatation after induction of anesthesia suggests that the primary alteration in caliber of the peripheral vessels is an expression of release of normal vasomotor tone, and is due to the action of the anesthetic agent on the vasomotor center. But the vasodilatation could also be due to a direct action of the anesthetic agent on the walls of the blood vessels.

The development of relative vasoconstriction in the later stages of the major operations probably expresses a circulatory readjustment for maintenance of the blood pressure. It occurs despite the fact that the amount of anesthetic used increases in proportion to the length of the operation. There is a limit to the duration and degree of vasoconstriction that can occur during lengthy major operations. This limit has not been determined, and may indeed vary from patient to patient. But it can be inferred that intense and prolonged vasoconstriction is indicative of maximal compensation and presages overt clinical shock.

BERNSTEIN

Peirce, E. C., II: Experimental Right to Left Pulmonary Blood Shunt in Dogs. Arch. Surg. **63**: 162 (Aug.), 1951.

The author describes a satisfactory method of producing a right to left pulmonary shunt in dogs. This consists of ligating and dividing all pulmonary vessels to the left lobes except the main pulmonary artery to the lower lobe and the largest lower lobe vein. The left bronchus is divided distally and closed with sutures, and then the lung is removed. An arterial segment preserved by refrigeration is inserted between the arterial and venous stumps.

ABRAMSON

Macpherson, A. I. S., Nabatoff, R. A., Deterling, R. A., Jr., and Blakemore, A. H.: Observations on the Use of Preserved Venous Hemografts in Experimental Aortic Defects. Arch. Surg. **63**: 152 (Aug.), 1951.

The behavior of venous segments grafted into the aorta, after storage under conditions calculated to preserve their viability, was studied in 22 dogs.

It was found that veins preserved by refrigeration at 4 to 6 C. in 10 per cent homologous serum and 90 per cent Simms times 7 solution could be used successfully to bridge aortic defects. When there was a conspicuous difference in the circumference of the aorta and of the venous transplant, laminated clot formed on the wall of the graft, as it would in a fusiform aneurysm. This was slowly organized and endothelized to form a smooth lining for the blood channel. In the wall of the graft itself some of the fibrous and elastic tissue generally persisted, while the cellular elements slowly degenerated. The intima was replaced by a fibrocellular layer from the host vessel, and the other layers by reactive ingrowth of fibroblasts from the perivascular tissues.

ABRAMSON

Rusted, I. E., Scheifley, C. H. Edwards, J. E., and Kirklin, J. W.: Guides to the Commissures in Operations upon the Mitral Valve. Proc. Staff Meet., Mayo Clin. **26**: 304 (Aug.), 1951.

The lack of well-defined anatomic guides has been one of many problems confronting the surgeons who have attempted to relieve mitral stenosis. This report is based on the anatomic features observed in a study of 250 hearts. Mitral stenosis was present in 50 of the 250 hearts. With great frequency, the papillary muscles were found to serve as guides to the sites of the commissures and thus may constitute an aid to the surgeon doing mitral commissurotomy. Chordae tendineae may also serve as guides to the commissures. The changes of rheumatic inflammation usually make these features even more pronounced than is the case in normal hearts.

SIMON

Edwards, E. A.: Functional Anatomy of the Porta-Systemic Communications. Arch. Int. Med. **88**: 154 (Aug.), 1951.

The portasystemic communications were studied by roentgenography and dissection, after injection of a barium sulfate suspension into the femoral veins, in three postmortem subjects with normal portal systems and in one with portal cirrhosis. In all, the injected material filled most of the portal system via the anastomoses existing in the pelvis, across the retroperitoneal surfaces of the abdominal viscera and in the mediastinum. The anterior parietal (periumbilical) channels were uninjected except in the patient with cirrhosis.

The present findings thus confirm the observations of eighteenth century anatomists of the normal patency of the portasystemic communications and the greater significance of the deep pathways. The veins comprising the deep communications are ordinarily multiple fine channels. Some connections of intermediate size (2 to 3 mm.) occasionally exist, especially between the inferior mesenteric, splenic or other visceral veins on the left side and the left renal vein or its tributaries.

The adequacy of the collaterals in extrahepatic and intrahepatic obstruction of the portal system is considered. The multiplicity of communications suggests that no one vessel is indispensable as a collateral pathway. Anatomically, however, special importance attaches to the ansatomoses in the region of the umbilicus and falciform ligament, the spleen, the left kidney and the rectum.

The utilization of the portasystemic communications in the collateral flow after hepatic vein or vena caval obstruction is discussed briefly. Although the portal and caval patterns of enlargement of the superficial veins of the trunk almost invariably show distinguishing features, a case is presented illustrating the portal type of pattern following obstruction of the inferior vena cava.

BERNSTEIN

THROMBOEMBOLIC PHENOMENA

Carter, J. F. B.: Reduction in Thrombophlebitis by Limiting Duration of Intravenous Infusions. Lancet **2**: 20 (July 7), 1951.

The author investigated the causes of thrombophlebitis following intravenous infusions. In those patients in whom the infusion period was greater than eight hours, the incidence of thrombus was 52 per cent, while in another group in which it was always less than eight hours, the percentage fell to 4.5.

ABRAMSON

Swanson, H. S.: Spontaneous Thrombosis of the Internal Carotid Artery. South. M. J. **45**: 705 (Aug.), 1951.

Since the introduction of cerebral arteriography, spontaneous thrombosis of the internal carotid artery has been noted more frequently. The pathogenesis of this disease has not been established, although atheromatous changes are probably the basis for the thrombus. The age incidence varies considerably, but most cases fall in the third to fifth decade. There is a great preponderance of males affected and the left side is involved about seven times as often as the right. The clinical picture resembles that of other cerebrovascular accidents. In about two-thirds of the cases, cerebral symptoms initially are transient, generally mild and suggest so-called "cerebrovascular spasm." After a period of months, or even years, a severe episode may result in severe incapacitation or death. Unilateral headache is a frequent early symptom. The lesions are predominantly encountered within the area of supply of the middle cerebral artery and particularly in the anterior central portion of this area. Therefore spastic hemiparesis is frequent. The spinal fluid is usually normal. The diagnosis is established by angiography. The author reports on six cases, two in some detail. If the diagnosis can be made early, excision of the damaged segment of the artery is advisable and anticoagu-

lants should be administered to prevent embolic complications.

WAIFE

VASCULAR DISEASE

Grice, K. J., and Maxwell, W. M.: Pulmonary Insufficiency: Circulatory Aspects. Proc. Roy. Australasian College Physicians **6**: 14 (Jan.), 1951.

The circulatory aspects of pulmonary insufficiency were studied by cardiac catheterization in 18 patients with chronic hypertrophic vesicular emphysema. The pressures found in the right side of the heart in cases of emphysema without heart failure were normal. In the presence of right ventricular failure, there was elevation of the ventricular pressure and of the mean intra-auricular pressure, as well as of the peripheral venous pressure. The right heart pressure was found to be lower in the sitting position than in the supine position, in opposition to the views of Sir Thomas Lewis.

Cardiac output in cases of emphysema without failure is also normal. The findings of McMichael and Sharpey-Schafer on cardiac output, the lack of value of digitalization in right heart failure and of the presence of a "hyperkinetic circulation" in patients with emphysema were not confirmed. They believed the fullness of the neck veins to be mechanical, due to a rise in intrapleural pressures from negative values to those approaching zero. The circulation times were normal.

BERNSTEIN

ERRATA

In the article "Blood Lipids and Human Atherosclerosis," by Dr. John W. Gofman and associates (**5**: 119, 1952), the following change should be read in table 1: the Mean Serum Cholesterol Level for normal males in the 41–50 year age group should be 260 ± 53.

In the article "Surgery for Mitral Stenosis. A Review of Progress," by Dr. Edward F. Bland (**5**: 290, 1952), the following changes should be read in table 2: the footnote "†Operations by Drs. J. G. Scannell and R. Warren" applies to the entry "Author's series (Boston)" rather than to the "Totals." Please note that Dr. Warren has no middle initial.

BOOK REVIEWS

Clinical Physiology and Pathology. *Ferdinand Hoff.* Stuttgart, Georg Thieme, 1950. (Agents: Grune & Stratton) 782 pages, 124 figures, $9.40.

The author gives a short historical review of the main concepts of disease since Hippocrates and stresses the necessity to consider always the whole body and not a single system. Emotional and physical mechanisms are a unit. The chief pathologic conditions encountered in the different organ systems are then enumerated without going into any detailed discussion of pathology and physiology. The cardiovascular system is discussed in 100 pages. A separate chapter is devoted to neurovegetative regulations, a subject in which the author is particularly interested.

This book should give the undergraduate student a synoptic review of the abnormalities encountered in the clinic.

D. SCHERF

Heart Disease in Pregnancy. *A. Morgan Jones.* New York, Grune & Stratton, 1951. 57 pages, 3 figures (6 plates), 7 tables. $1.50.

As Crighton Bramwell states in the foreword of this brief but comprehensive monograph, Dr. Jones is to be congratulated on having made a valuable contribution to our knowledge of the subject. He has made a very careful study of a large group of cases (485) followed through pregnancy of which 352 were observed for periods up to several years after confinement.

In this unusually well written and systematically organized monograph the author has correlated clinical aspects with the physiologic changes in the circulation during pregnancy in the normal subject as well as in the patient with organic heart disease. This makes it possible for physicians to appreciate the nature and extent of the burden that pregnancy imposes on the structurally impaired heart and yet be fully aware of the ways in which the normal circulatory changes of pregnancy can simulate organic heart disease.

This concise study, which is well organized and clearly presented, covers all the essential features of heart disease in pregnancy, including among others diagnosis of organic heart disease during pregnancy, the causes of maternal death, the assessment of fitness for pregnancy in which the author employs a classification similar to the criteria endorsed by the American Heart Association, the management of termination, antenatal supervision with emphasis on the prevention, early recognition and efficient treatment of heart failure, and lastly the management of confinement. In the latter chapter the author stresses the inadvisability of inducing premature labor and reviews the relative risk of caesarian section and vaginal delivery. He clearly shows that the former is very rarely indicated for cardiac reasons but that it may be justified, when severe heart disease is present, for less than the usual obstetrical reasons to avoid the risks of a difficult confinement.

In a concluding chapter on the effect of pregnancy on the course of rheumatic heart disease, which accounted for some 90 per cent of the patients in his case load, the author very aptly quotes verbatim the opinion of his mentor, Crighton Bramwell, that "it is often a matter of probability rather than certainty whether the deterioration in the patient's condition, over a period of years, is attributable to the incidence of pregnancy or merely to the natural course of the disease." In other words there is still no evidence that pregnancy leads to more than a transient deterioration in the cardiac status or that repeated pregnancies appreciably shorten life.

Although the bibliography is good and fairly complete, it omits reference to an article which I consider very pertinent to the subject covered in this monograph, namely that of Bunim and co-workers: The Determination of the Prognosis of Pregnancy in Rheumatic Heart Disease, published in the American Heart Journal (**35**: 282–297, 1948).

This is an excellent little book which the reviewer recommends without reservation both to physicians and to medical students.

Drug Therapy of Cardiac Diseases (Arzneitherapie der Herzkrankheiten). *Hans Jürgen Oettel.* Stuttgart, Georg Thieme, 1951. (Agents: Grune & Stratton) 253 pages, 15 figures. $6.50.

The author discusses in the first section, comprising 117 pages, the different drugs used in the treatment of cardiac patients. In the second section the therapy of different cardiac diseases is dealt with. In small final sections the therapy of dyspnea and of edema is described. There are no references.

Many statements of the author, put forward as facts without substantiation, will not be accepted by the American cardiologist. It is maintained that G-strophanthin dilates while K-strophanthin narrows the coronary arteries. "Light" angina pectoris and coronary sclerosis are indications for therapy with digitalis. The electrocardiograph should be taken repeatedly during the administration of digitalis in order to avoid depression of the RS-T segments. The author believes that prophylactic digitalization before surgery is of "extraordinary" importance. He recommends it in the healthy before electro- or insulin-shock therapy. In paroxysmal tachycardias a rate of the ventricles of over 240

causes death within one hour. In this condition quinidine is not recommended but digitalis is the therapy of choice. Cardiac glycosides exert a direct diuretic action. Digitalis is indicated in dissociation with interference. In myocarditis the treatment should consist in small doses of digitalis with an intravenous infusion of "physiologic doses" of insulin and acetylcholine.

The style is verbose and tiring. The great tradition of classic European cardiology is conspicuously absent from this book.

SCHERF

Modern Precordial and Extremity Leads in Practice (Die neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis). *Herbert Reindell and Helmuth Klepzig, with a foreword by Ludwig Heilmeyer.* Stuttgart, Georg Thieme, 1951. (Agents: Grune & Stratton) 179 pages, 64 figures, 6 tables. $5.35.

The primary purpose of this book is to introduce the German-speaking reader to the accomplishments of unipolar electrocardiography published in Anglo-American journals since the beginning of the last war. This objective is accomplished in a very satisfactory manner. More important for the American reader are the personal observations and interpretations of the authors, one of whom, Dr. Reindell, has had extensive experience with precordial leads for the last 15 years.

The authors give a detailed statistical study of the normal range of precordial leads in 100 normal subjects and 40 athletes, including the important but seldom studied ratios R/S and R/T as well as the difference in the time of appearance of the intrinsicoid deflections between leads V_6 and V_1. In 30 cases the electrical position of the heart was compared with the roentgenologic position in two planes; the electrical position was always found more vertical than the anatomic position. Of especially great importance are the numerous correlations between the electrocardiographic pattern and the localization of myocardial infarction and areas of necrosis, as studied histologically by Prof. F. Büchner. Of these, one case of kyphoscoliosis with right ventricular failure showed pathologic Q waves in leads V_1 to V_3; histologic study disclosed myocardial necroses in the anterior wall of the right ventricle. The paper, binding and the reproduction of the tracings are excellent; most of the latter were taken with three synchronous leads. A bibliography of 10 pages and author and subject indexes complete the work.

E. LEPESCHKIN

Blood Clotting and Allied Problems. Transactions of the Third Conference. *Edited by Joseph E. Flynn.* New York, Josiah Macy, Jr., Foundation, 1950. 224 pages, 31 tables, 51 figures. $3.00.

The *Transactions* of the Conferences on Blood Clotting and Allied Problems held by the Josiah Macy, Jr., Foundation are records of informal discussion meetings of a group of active investigators, both clinical and laboratory, under the chairmanship of Irving S. Wright. The third conference centers around certain newer anticoagulants and methods for the control of anticoagulant therapy, but such meetings lead naturally to presentation of a diverse selection of material of current interest.

Phenylindanedione is a drug which has an action similar to that of dicumarol but one that is of much briefer duration; the same is true to a lesser extent of Tromexan. This may or may not be an advantage, depending on the plan of therapy to be followed. Jaques draws an analogy between the different dicumarol-like drugs and the different insulin preparations which vary in their duration of action. Paritol, a synthetic anticoagulant of the heparin type, is cheaper than heparin and has a more prolonged action, but occasionally produces severe allergic reactions.

By means of radioactive dicumarol, Jaques and his colleagues show that this drug is retained in the liver for a brief period; vitamin K seems to hasten its removal from this organ. A puzzling feature of these experiments is the fact that the effect on the prothrombin time increases as dicumarol leaves the liver, and that this effect reaches its peak after the drug is mostly gone. Whether or not this is due to the activity of metabolic products of dicumarol remains to be determined.

Brambel leads the discussion of the highly controversial topic of prothrombin tests. Evidence is brought forward that the prothrombin time does not measure prothrombin in the sense of the substance which is converted into thrombin and determines the yield of thrombin measured by the two-stage method. It is furthermore uncertain exactly what the prothrombin time does measure. Quick continues to regard the prothrombin time as a measure of prothrombin, but he defines prothrombin essentially in terms of the prothrombin time and without use of the criterion of measurable yield of thrombin. This disagreement on such a basic matter as the definition of prothrombin is sufficient indication of the complexity of the subject. At the same time, there is agreement as to the importance of the prothrombin time in the control of dicumarol therapy. Understanding of this test, and not of its mere mechanical performance, is needed for its intelligent use.

Prothrombin tests on serum are discussed by Brinkhous, Quick and Alexander, from their individual points of view. This work finds important practical application in the demonstration of the differences between normal and hemophilic serum, whatever the differences may be. Tocantins presents additional evidence on his own, equally interesting, approach to the study of hemophilia: the detection of an inhibitor of thromboplastin. A critical analysis

of technics of the two-stage method is provided by Ferguson.

The application of zeta-potential measurements to the study of blood coagulation is reported by Wood.

Like the transactions of the two preceding conferences, this book has the most valuable feature of frank, informal exchange of opinion between research investigators, some of whom in their publications hardly seem even to speak the same language. Under these circumstances, the coherence and readability of the transactions are altogether remarkable, and are greatly to the credit of the editor.

FRANK D. MANN, M.D.

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

AMA EXIBIT

The Association will be represented at the Annual Meeting of the American Medical Association in Chicago, June 9 to 13, by several exhibit booths and a series of daily "Question and Answer" sessions on various phases of heart disease.

The exhibit will be presented in conjunction with the Illinois and Chicago Heart Associations and will demonstrate how the associations aid the physician in the prevention, diagnosis, treatment and management of the cardiovascular diseases. There will be a visual summary illustrating highlights of the achievements of the Association's research support program. Publications issued by the Association, which are designed to help the physician, also will be displayed.

The new series of heart models produced by the Association as visual aids in the undergraduate and postgraduate education, as well as for the teaching of fluoroscopy, will also be exhibited.

STIPEND INCREASES

The Research Committee of the Association's Scientific Council recently voted to increase the stipends granted to Research Fellows and Established Investigators. Under the new scale, Research Fellows will start at $3,500 with increments to reach a maximum of $5,500, and Established Investigators will be started at $6,000, with increments up to a total of $9,000.

NEW AFFILIATE

The Board of Directors of the Association has approved the affiliation of the Mississippi Heart Association.

HEART BULLETIN

The first issue of the bimonthly Heart Bulletin, designed particularly for the physician in general practice, appeared in March.

The bulletin is published by the Medical Arts Publishing Foundation of Houston, a nonprofit service organization affiliated with the University of Texas.

Paul D. White, M.D., Boston, is Chairman of the Advisory Board, members of which were selected in cooperation with the Association and the National Heart Institute. R. Lee Clark, Jr., M.D., is the editor.

The Bulletin is available through subscriptions purchased by a local or state agency—an affiliated Heart Association, State Medical Society, or State Health Department—for the physicians in the state.

This bulletin does not duplicate any publication of the Association.